Anesthetic and Analgesic Drug Products Advisory Committee Meeting

FDA Introductory Remarks

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Food and Drug Administration
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Objective

- Discuss the risk of serious neurologic adverse reactions associated with epidural steroid injection (ESI) administered to reduce inflammation for pain management
- Focus on safety
- Potential regulatory options

Introduction

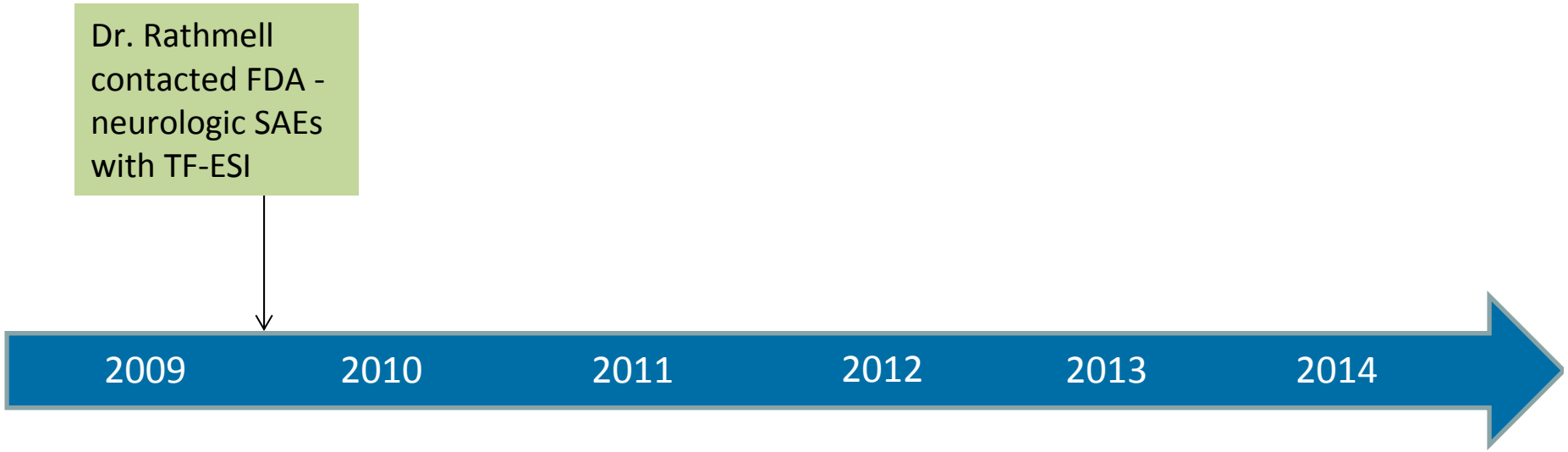
- ESI common procedure for management of spinal pain syndromes
- FDA has approved several injectable corticosteroids for a variety of indications
- Corticosteroids are not approved for epidural administration
  - a sponsor would need to submit an application with data to demonstrate efficacy and safety of ESI
  - off label use of approved products, practice of medicine
- FDA has been evaluating the risk of serious neurologic events with ESI

Challenges in Assessment of Risk of ESI

- ESI is complicated procedure
  - different approaches – interlaminar, transforaminal, caudal
  - +/- concomitant administration of anesthetic
  - +/- imaging
  - difficult to separate risk of procedure vs. risk of drug
- Off-label use → impacts risk/benefit assessment
- Practicing community categorization of injectable corticosteroids into particulates vs. non-particulates
- Compounded products are sometimes used

Regulatory History

Regulatory History



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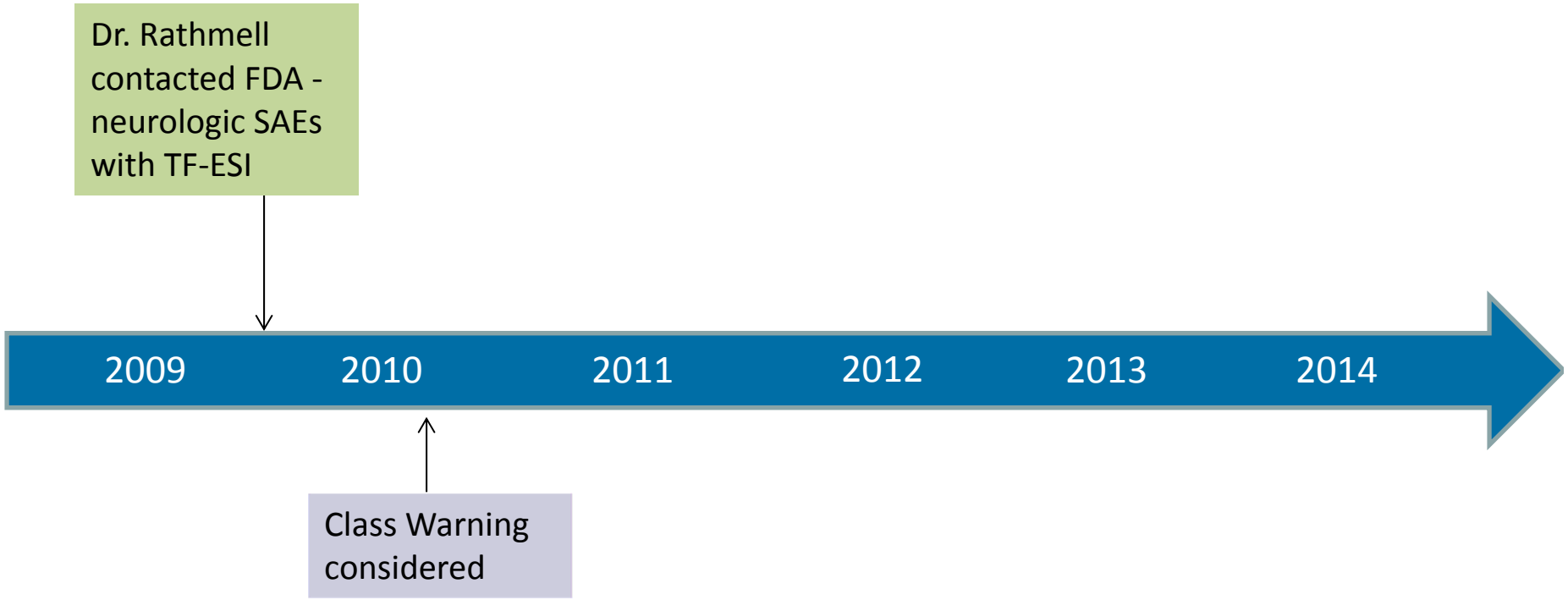

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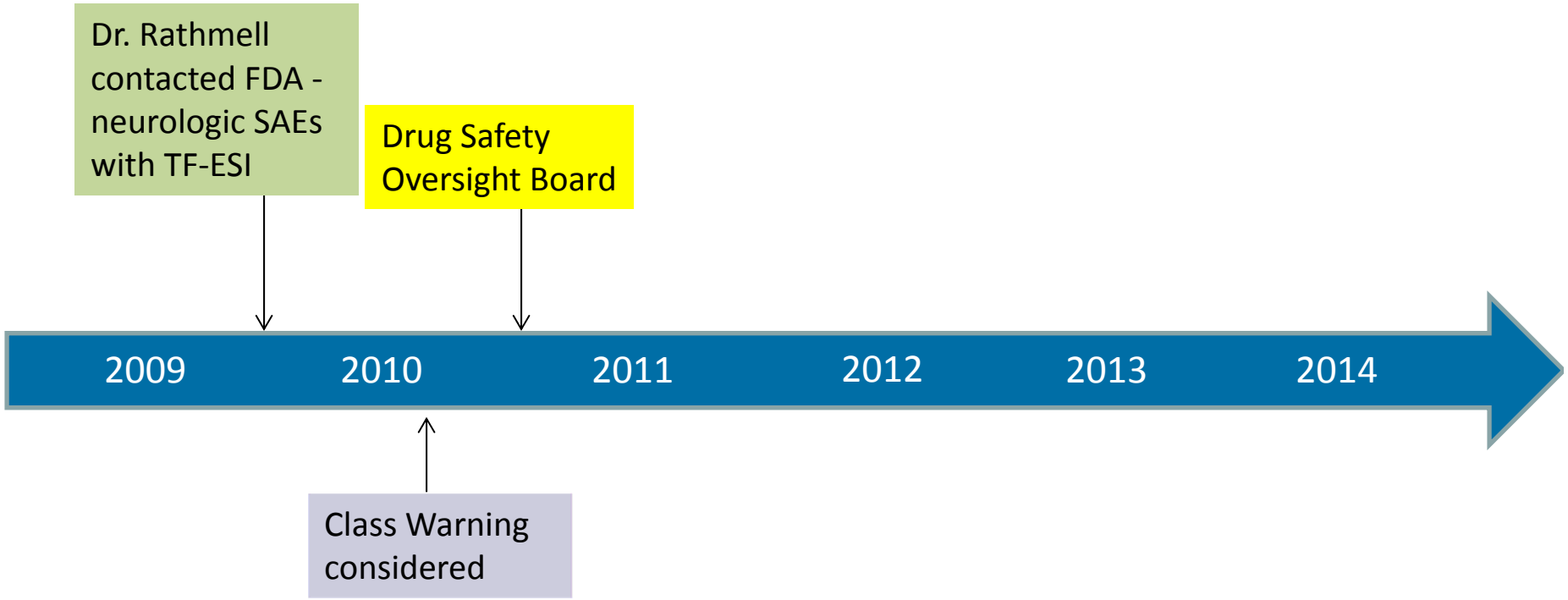

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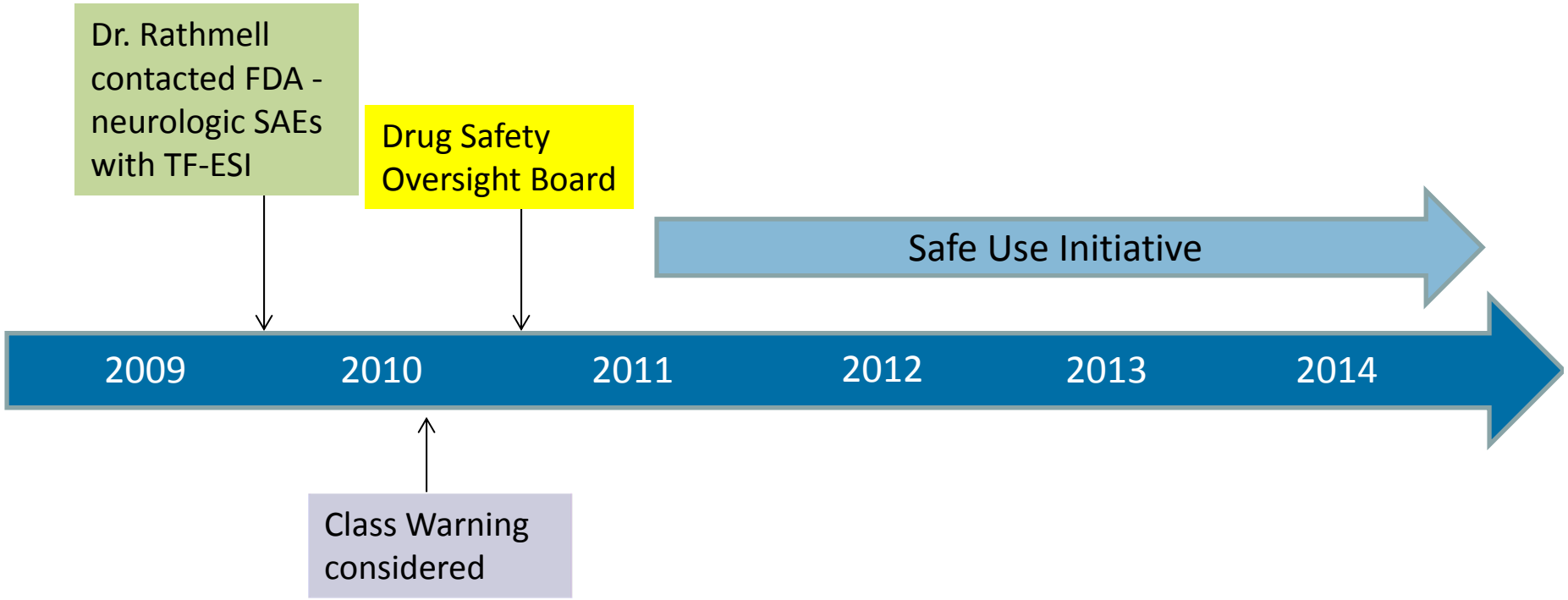

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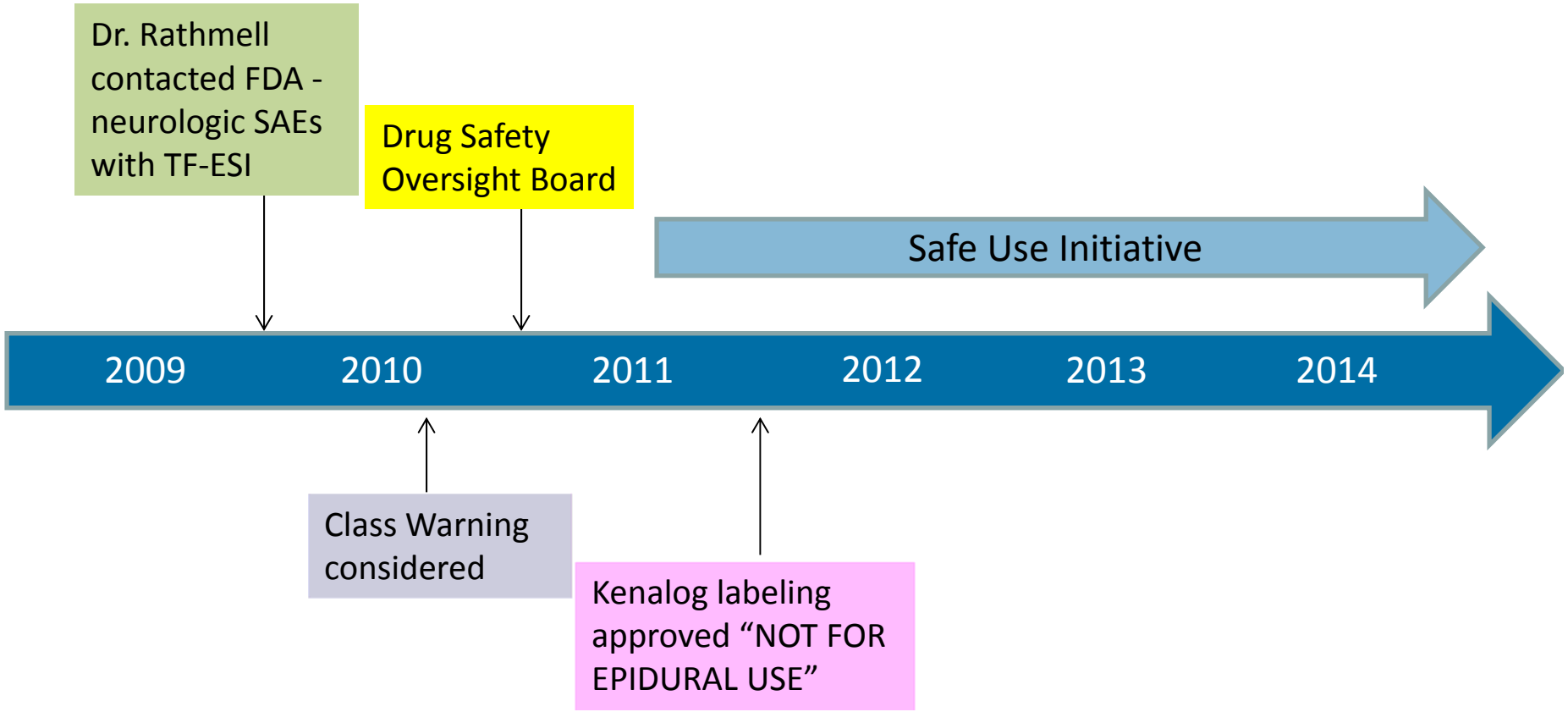

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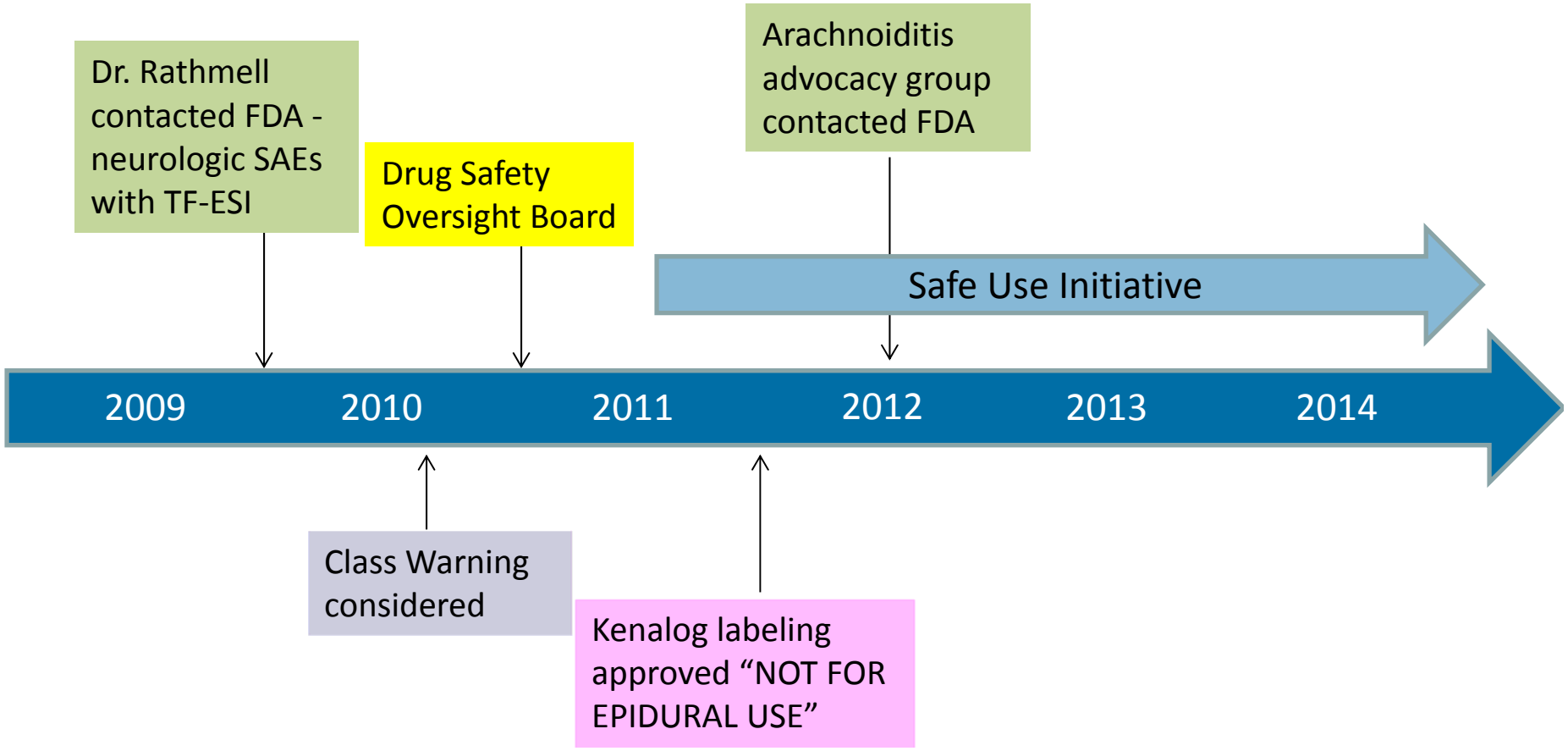

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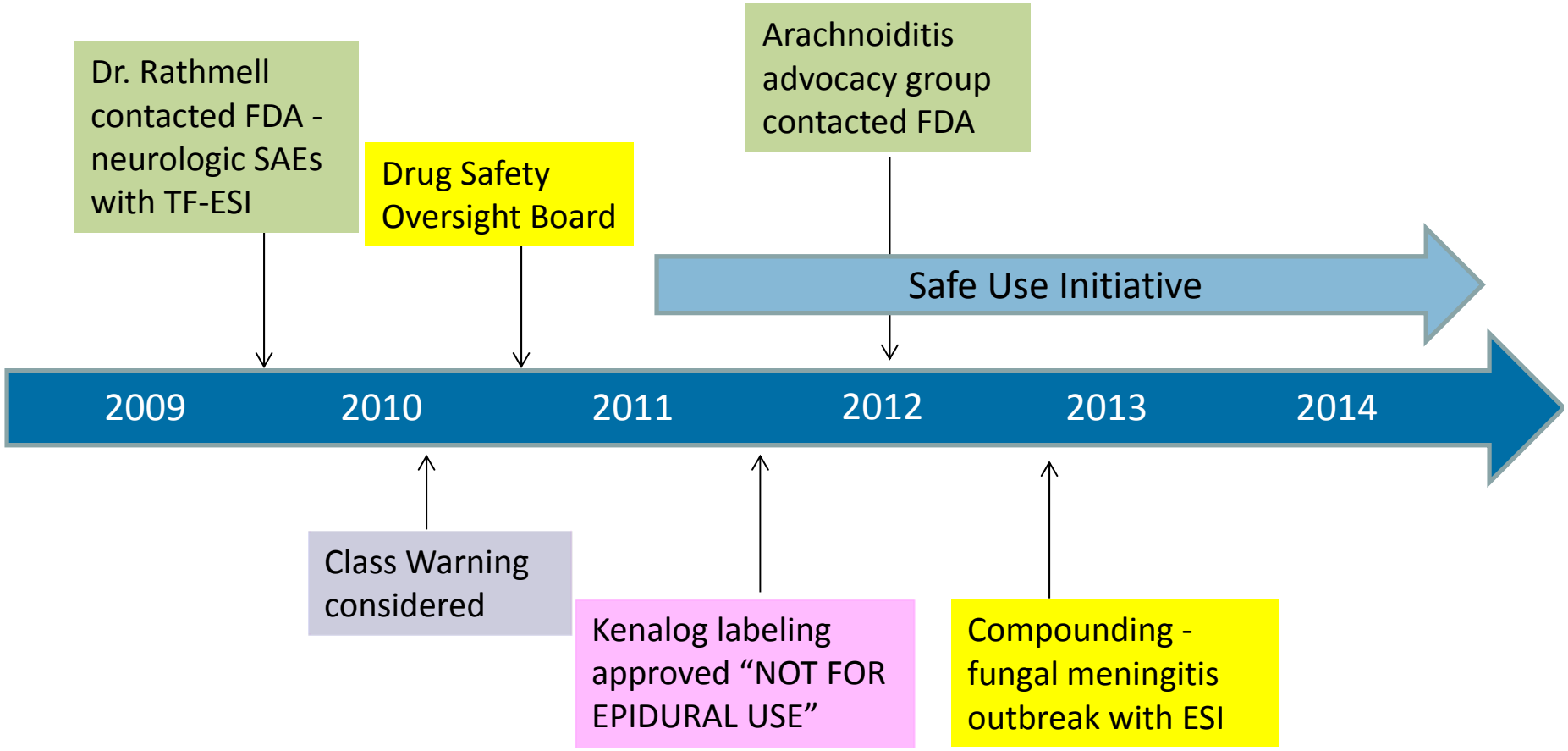

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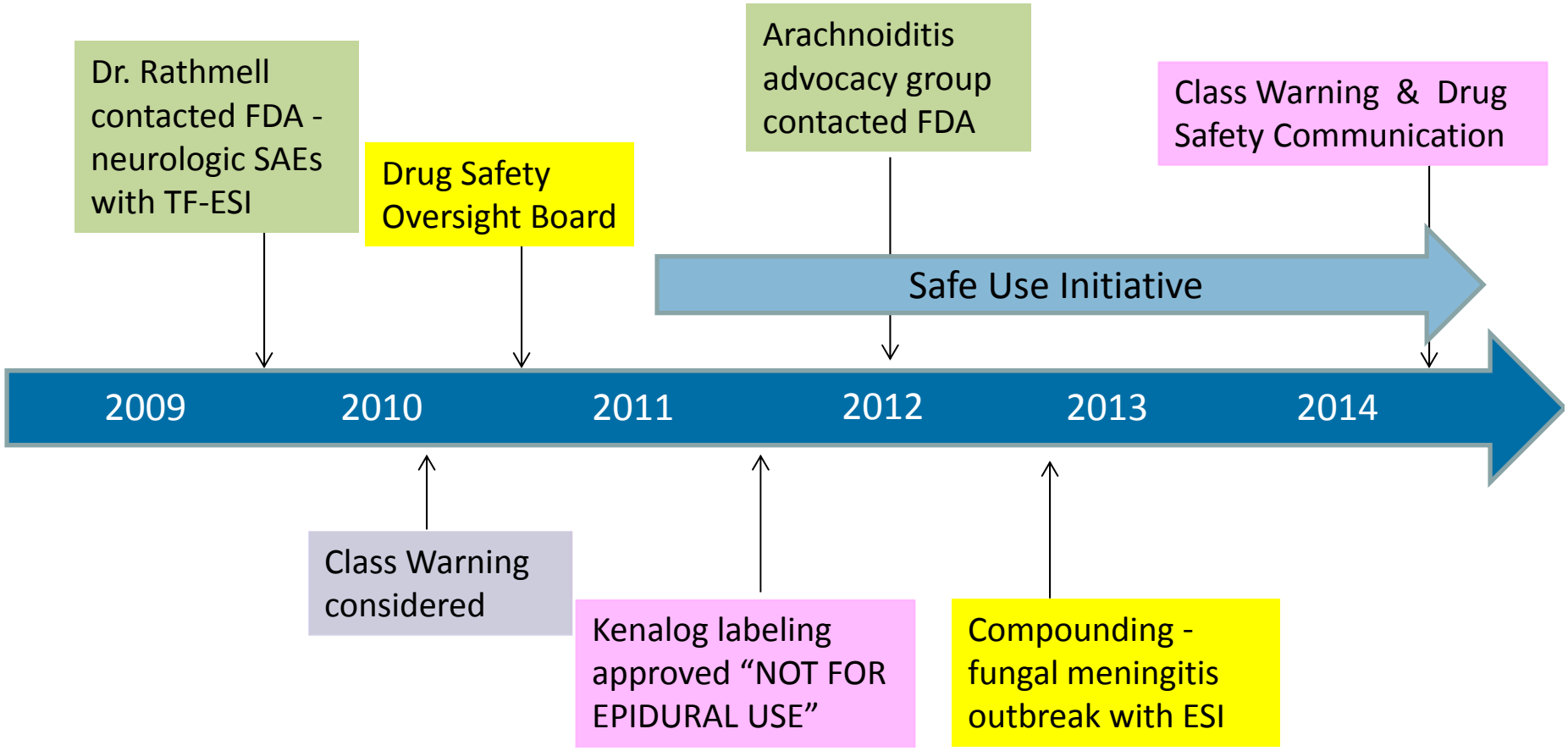

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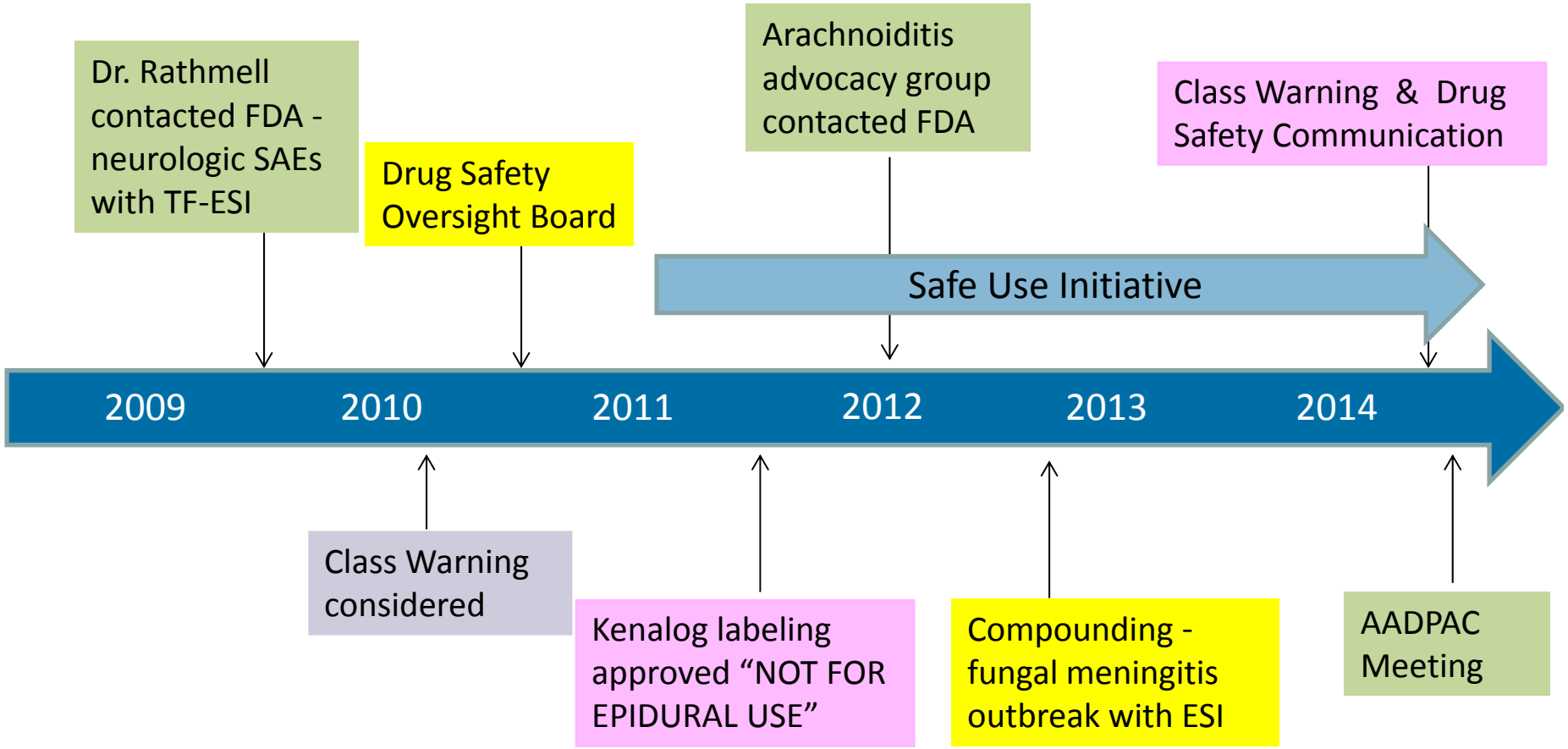

Relevant Corticosteroid Labeling

- Class Warning – July 2014

WARNINGS —

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

Relevant Corticosteroid Labeling

- Most injectable corticosteroids have Warning or Contraindication for intrathecal injection

- Kenalog-10 and -40 (triamcinolone acetate)

  NOT FOR INTRAVENOUS, INTRADERMAL, INTRAOCULAR, EPIDURAL, OR INTRATHECAL USE

- Some countries have contraindicated the epidural use of some corticosteroids

- One of the issues for panel discussion today is labeling and specifically whether a contraindication is warranted

Approved Injectable Corticosteroids

Corticosteroid	Tradename	Sponsor	Suspension or Solution	Solubility in H_2O	Notable Excipients
Betamethasone acetate, betamethasone sodium phosphate	Celestone Soluspan	Merck Sharpe Dohme	suspension	acetate insoluble; sodium phosphate soluble	benzalkonium chloride
Dexamethasone sodium phosphate	Hexadrol	Organon	solution	freely soluble	benzyl alcohol
Hydrocortisone sodium succinate	Solu-Cortef	Pharmacia and Upjohn (Pfizer)	powder for solution	very soluble	benzyl alcohol
Methylprednisolone acetate	Depo-Medrol	Pharmacia and Upjohn (Pfizer)	suspension	insoluble	benzyl alcohol polyethylene glycol
Methylprednisolone sodium succinate	Solu-Medrol	Pharmacia and Upjohn (Pfizer)	powder for solution	soluble	+/- benzyl alcohol
Triamcinolone acetonide	Kenalog-10 Kenalog-40	Apothecon (Bristol Myers Squibb)	suspension	insoluble	benzyl alcohol
Triamcinolone diacetate	Aristocort (Forte)	Sandoz	suspension	insoluble	benzyl alcohol
Triamcinolone hexacetonide	Aristospan	Sandoz	suspension	insoluble	benzyl alcohol

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Triamcinolone acetonide	Kenalog-10 Kenalog-40	Apothecon (Bristol Myers Squibb)	suspension	insoluble	benzyl alcohol
Triamcinolone diacetate	Aristocort (Forte)	Sandoz	suspension	insoluble	benzyl alcohol
Triamcinolone hexacetonide	Aristospan	Sandoz	suspension	insoluble	benzyl alcohol

Particulate vs. Non-Particulate

- Terminology in medical literature to classify corticosteroids for ESI
- FDA does not use particulate and non-particulate terminology
  - FDA uses suspension or solution for injectable corticosteroids
- In medical literature, some suggest risk and benefit may differ between particulate and non-particulate corticosteroids for ESI
- FDA has been criticized for class Warning in part because we did not differentiate between particulate and non-particulate products

Compounding

- Compounded drugs are not FDA approved, but they are exempt from certain statutory requirements including the new drug approval requirements if all conditions described in the following are met:
  - section 503A (applicable to licensed pharmacies, physicians, and Federal facilities) or
  - section 503B (applicable to outsourcing facilities, which may or may not be licensed pharmacies)

- Because compounded drugs are not FDA approved, they have not been reviewed for safety or effectiveness, and FDA has not reviewed or approved their labeling.
  - we cannot assess utilization
  - we do not have information on formulations

Compounding

- Some observed adverse events with compounded ESIs have been associated with contamination caused by poor sterile practices by compounders
- FDA has been increasing its oversight of sterile compounding
- We recognize that compounded products are sometimes used for ESI, but compounding is not a focus of discussion at this AC meeting.
- This AC meeting will focus broadly on the use of ESIs and their safety and efficacy

Role of FDA

- For approved products, FDA reviews and approves the labeling, and can direct sponsors to make safety-related labeling changes after approval if we determine they are necessary.
  - FDA required a class Warning approved in July 2014

- Sponsors can propose safety labeling regarding epidural use
  - Kenalog-10, Kenalog-40 – "NOT FOR EPIDURAL USE"
  - contraindication for epidural use of corticosteroids in some countries

- Communication of safety issue

Role of FDA

- While FDA does not regulate the practice of medicine, we understand our actions can influence the practice of medicine

- Safe Use Initiative
  - organized an *external* expert panel to address safety concern with goal to reduce preventable harm
    - developed clinical considerations for ESI
    - intended for healthcare providers, not FDA

- Improve oversight of compounding

- Convene this Advisory Committee meeting to have open discussion of safety issue
  - discuss regulatory options

Agenda

- Guest Speakers
  - Dr. Steven Cohen – efficacy of ESI
  - Dr. Charles Argoff – safety of ESI
- FDA Presentations
  - FAERS review
  - Analysis of extent of ESI procedure
  - Literature review
  - Safe Use Initiative
- Expert Panel Findings – Dr. James Rathmell
- Open Public Hearing
- Charge to the Committee
- Committee Discussion

Note

No sponsor presentations

No FDA presentation on efficacy

Topics for Discussion

- Benefits of epidural steroid injections
- Risks of epidural steroid injections, particularly neurologic events
- Voting question on contraindication for epidural use of injectable corticosteroids
  - labeling recommendations
- Additional recommendations

Epidural Steroid Injections (ESIs) Postmarketing Serious Neurological Adverse Events Reported to the FDA Adverse Event Reporting System (FAERS)

CDR Laurelle Cascio, Pharm.D.
CDER|OSE|OPE|Division of Pharmacovigilance II
November 24, 2014

Outline

- FDA Adverse Event Reporting System (FAERS)
  - Background
  - OSE postmarketing regulatory activities
  - Overview of spontaneous reports of serious neurologic events
  - Examples of FAERS cases of serious neurological events
  - Overview of spontaneous reports of arachnoiditis
  - Examples of FAERS cases of arachnoiditis

Background: FAERS

- FDA computerized database
- Spontaneous adverse event reports
- Human drug and therapeutic biologic reports
- Consumers, patients, health care providers, manufacturers
- U.S. and foreign reports

Background: FAERS (cont.)

- Strengths
  - events not seen in clinical trials, all uses, broad patient population, risk factors, populations at risk
- Weaknesses/Limitations
  - not suitable for events with high background rate, worsening of pre-existing disease, comparing drugs in same class, drug interactions
  - underreporting, poor quality reports, reporting bias, duplicates
  - cannot be used to calculate incidence rate

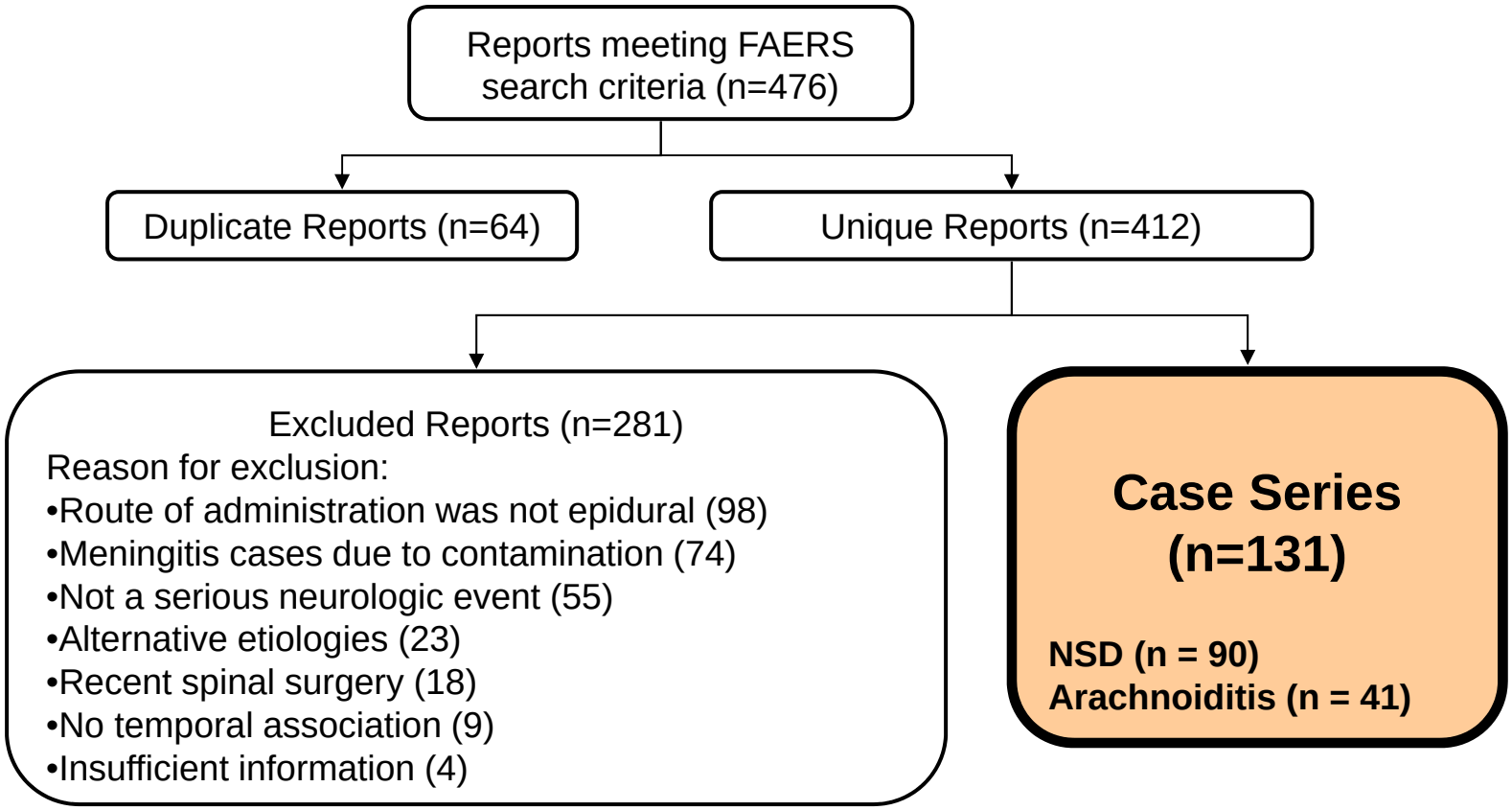
FAERS Overview of Spontaneous Reports of ESI Serious Neurologic Adverse Events

FAERS Search Strategy

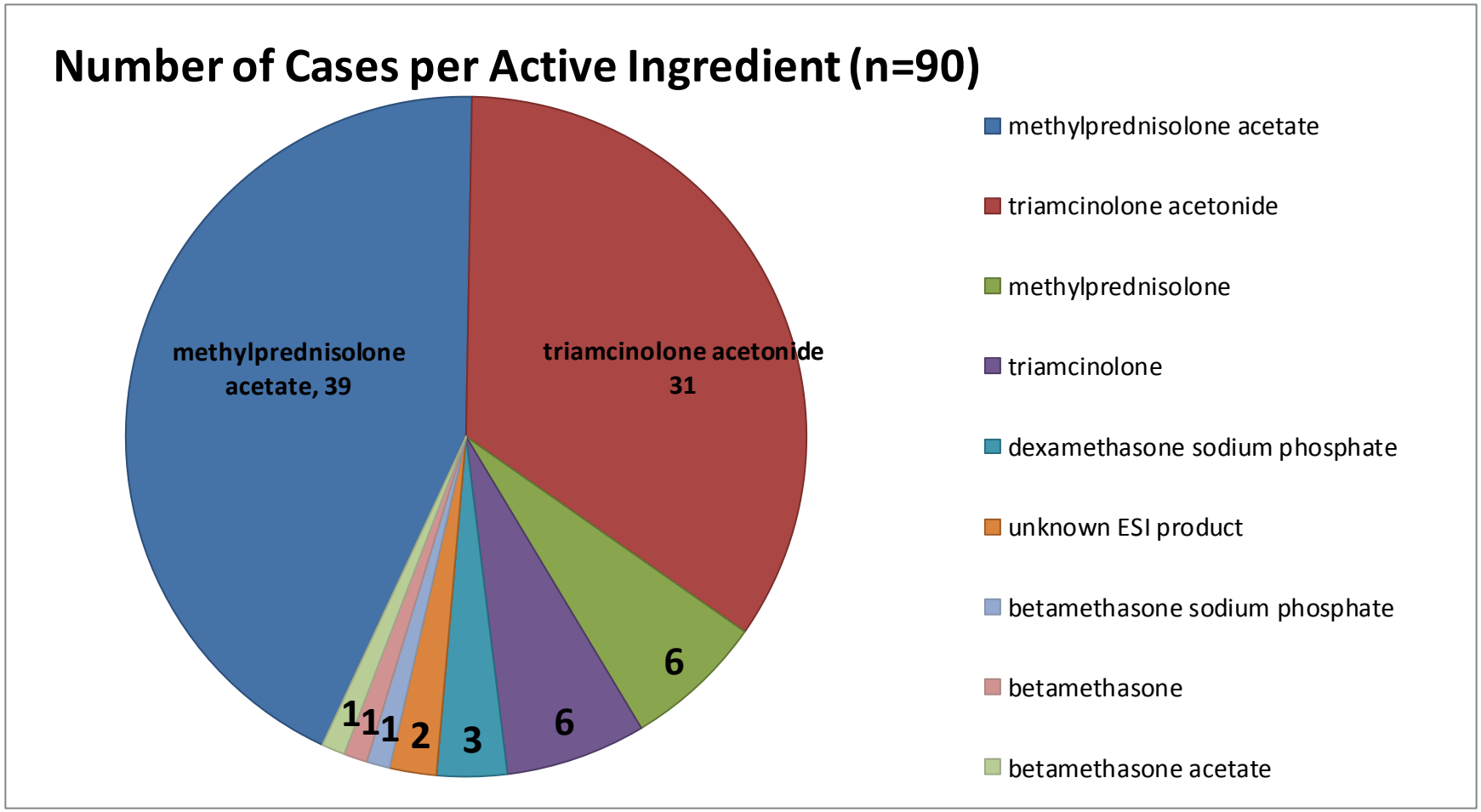
FAERS Search Strategy		
Date of search	April 2014	
Search #	#1	#2
Search Terms	Nervous System Disorder	Arachnoiditis
Time period of search	11/1/1997* – 4/23/2014	1/1/1965 – 4/23/2014
Active Ingredients (all salt formulations)	betamethasone, dexamethasone, hydrocortisone, methylprednisolone, triamcinolone	
Other criteria	domestic; serious outcome^	
Narrative term search	epidural, transforaminal, translaminar, interlaminar, caudal	--

*FAERS search results do not display case narratives of reports submitted to FDA prior to November 1, 1997, therefore only reports submitted to FDA after this date were included so that narrative terms of interest can be searched.
^Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events

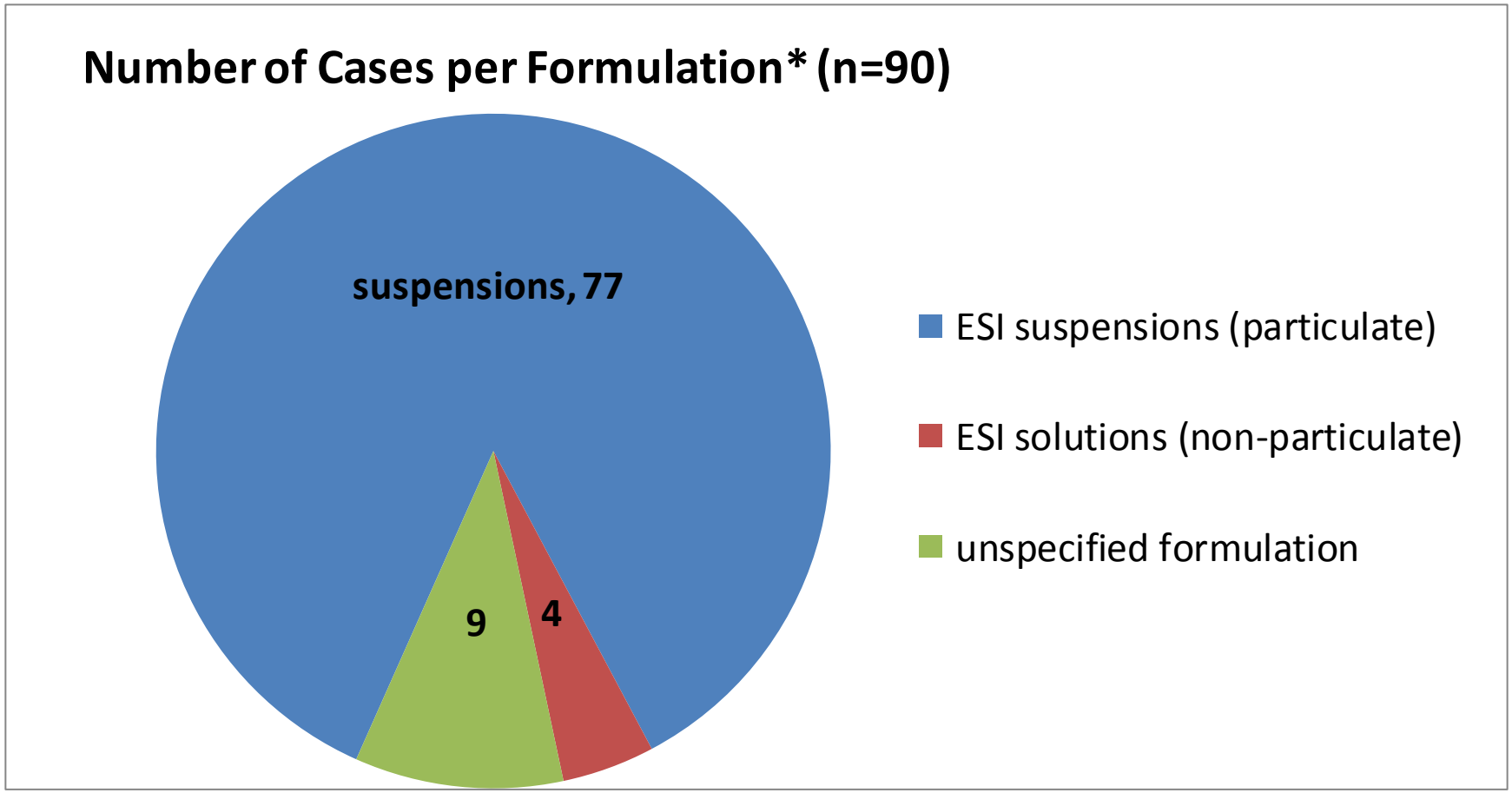
FAERS Case Selection



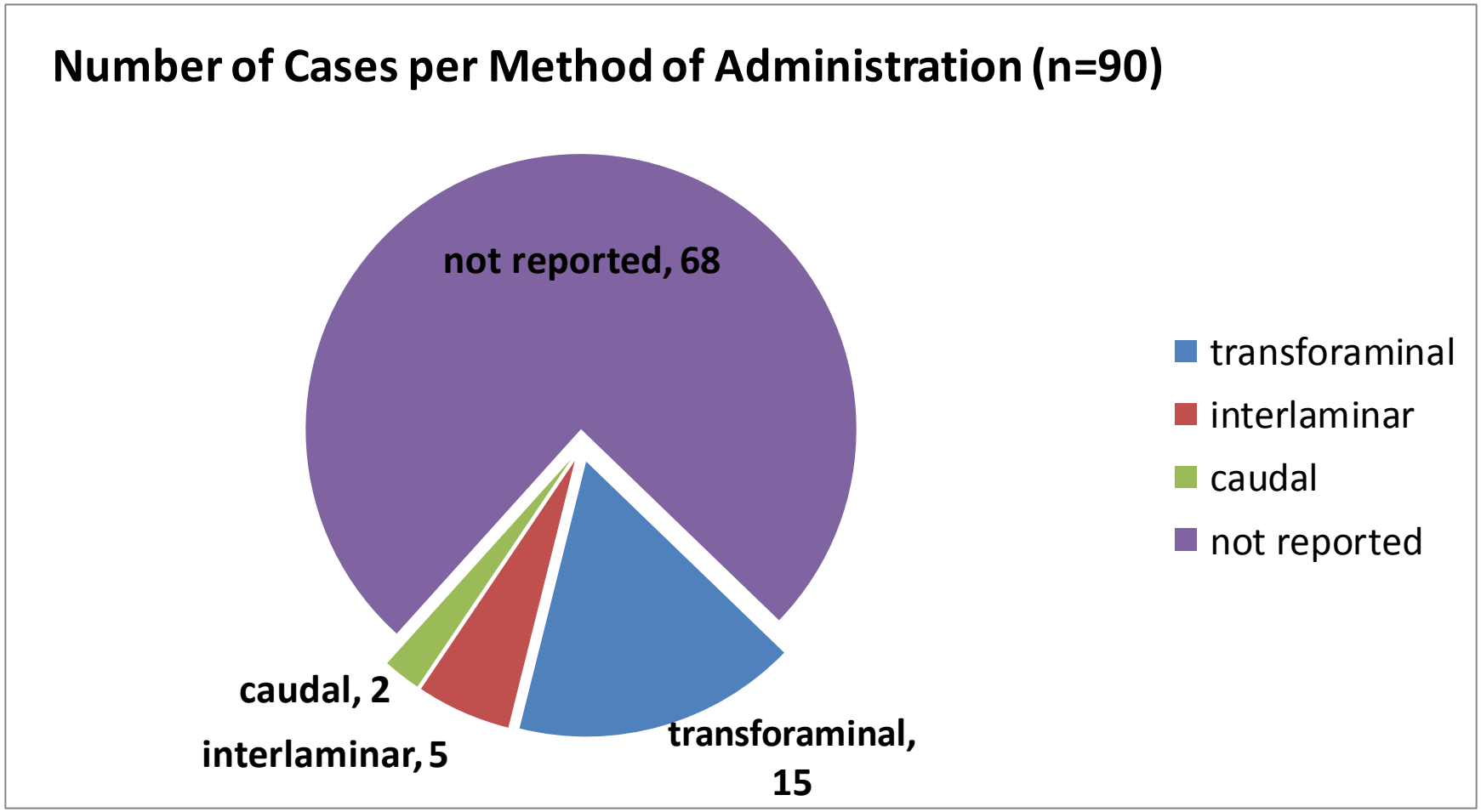
ESI Nervous System Disorder Cases



ESI Nervous System Disorder Cases



ESI Nervous System Disorder Cases



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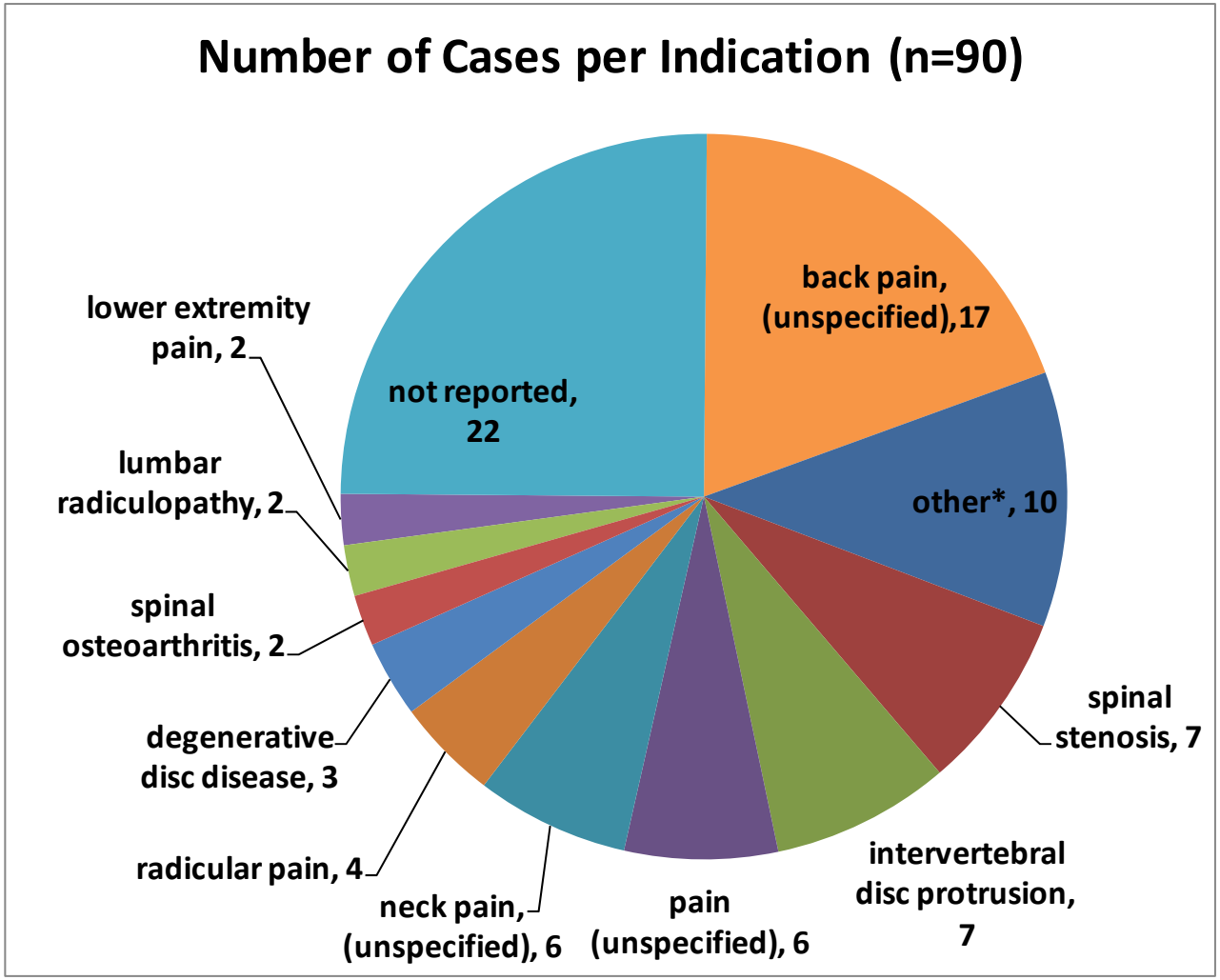
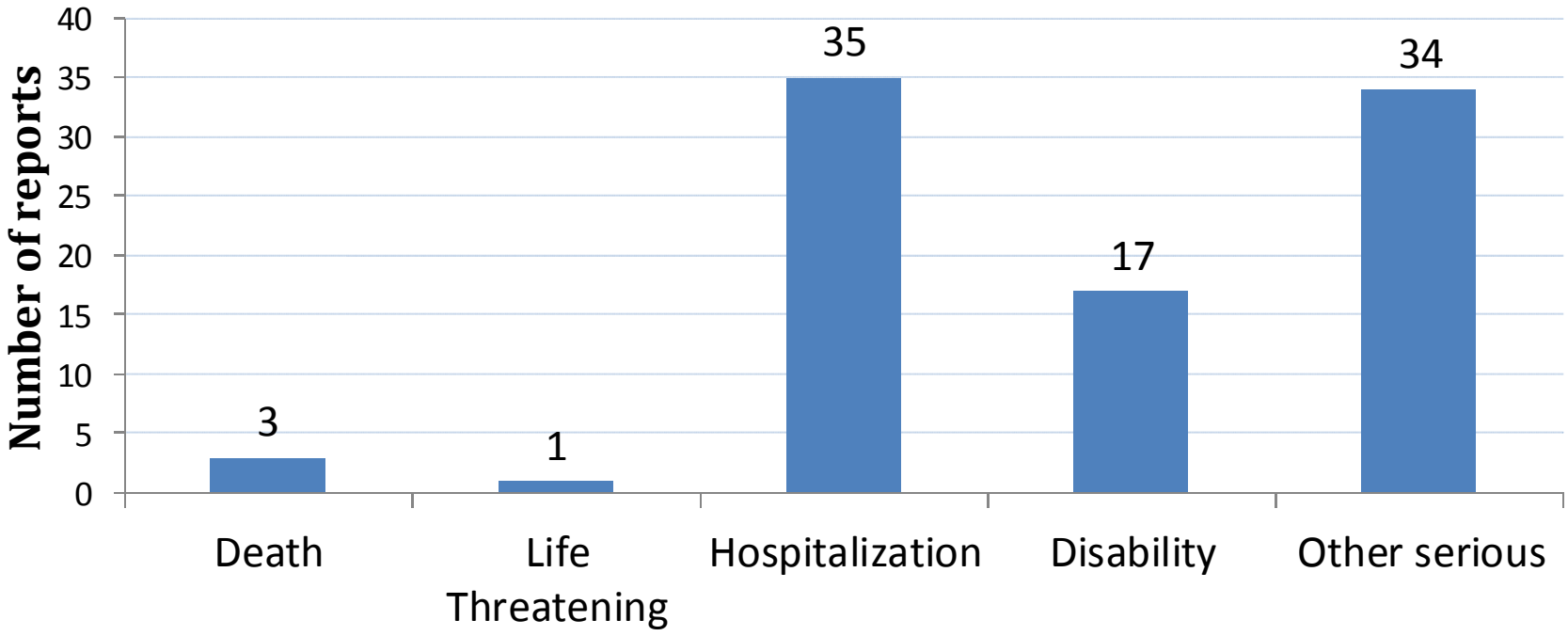


*<u>other (10)</u>

-upper extremity radicular symptoms (1)
-spinal disorder (1)
-cervical disc protrusions (1)
-neuritis (1)
-shoulder tendonitis (1)
-sciatica (1)
-migraine (1)
-herniated nucleus pulposus (1)
-cervical spondylosis (1)
-disc herniation (1)

ESI Nervous System Disorder Cases



^Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

Other Characteristics for ESI Nervous System Disorder Cases (n=90)

- Prior ESI (28)
- Concomitant anesthetics
  - bupivacaine (21), lidocaine (19), ropivacaine (1)
- Concomitant contrast dye/imaging
  - Contrast agent (23), fluoroscopy (21), CT (2), angiography (2)
- Time to onset of event
  - Within 1 day (47), 1 day – 1 month (13), >1 month (2)
- Reported possible etiologies for neurologic adverse event
  - Unintentional/suspected: intra-arterial (2), intra-arterial and movement of needle (1), intravenous (1), subdural space (1), cerebrospinal fluid (1); prior recent intrathecal injection (1)

Reported Events for Nervous System Disorder Cases

- Spinal cord infarction
- Paralysis
- Quadriplegia
- Paraparesis/paraplegia
- Stroke
- Bowel/bladder dysfunction
- Cauda equina syndrome
- Thrombosis/thromboembolism
- Sensory disturbances
- Blindness (transient and possible permanent)
- Seizures
- Psychological/behavioral changes

Examples of FAERS Cases of ESI Serious Neurological Events

Lumbar Transforaminal ESI

- 83 year-old female
- **Betamethasone sodium phosphate/acetate** (suspension) + bupivacaine
- No history of lower extremity numbness or weakness
- Fluoroscopy
- Immediately after, the patient experienced lower extremity numbness and weakness
- Diagnosis: **acute spinal cord infarction**
- Patient was recovering (partial motor recovery) at time of reporting

Kennedy et al. Paraplegia following image-guided transforaminal lumbar spine epidural steroid injection: two case reports. Pain Medicine 2009;10: 1389-1394.

Cervical Transforaminal ESI

- 53 year-old male
- **Triamcinolone** (dose and formulation unspecified)
- Contrast confirmed with fluoroscopy
- 10 to 15 minutes post-procedure, patient noted weakness in left arm and bilateral lower limbs
- MRI revealed a diffuse vascular infarct to the cervical cord
- **quadriplegia**

Ludwig M, Burns A, Stephen P, Spinal Cord Infarction Following Cervical Transforaminal Epidural Injection. Spine 2005; 30: 226-8

Cervical Interlaminar ESI

- 66-year-old female
- **Methylprednisolone** 80 mg (formulation unknown)
- Immediately after, she experienced spasm pain with no neurologic status changes
- Diagnosis**: spinal epidural hematoma** and **quadriplegia**
- Underwent bilateral C5-T6 laminectomy with epidural hematoma evacuation
- Event outcome unknown

Chang Chien GC, et al. Spinal epidural hematoma resulting in tetraplegia after cervical interlaminar epidural steroid injection and intramuscular ketorolac: A case report. Phys Med Rehabil 2012;4/10 Suppl 1:S320

Cervical Interlaminar ESI

- 58-year-old male
- **Betamethasone sodium phosphate** (dose unknown)
- Fluoroscopy
- One month later: **seizures, transient blindness, head pain, vertigo, confusion, muscle weakness, and mood changes**
- Event outcome unknown

Caudal ESI

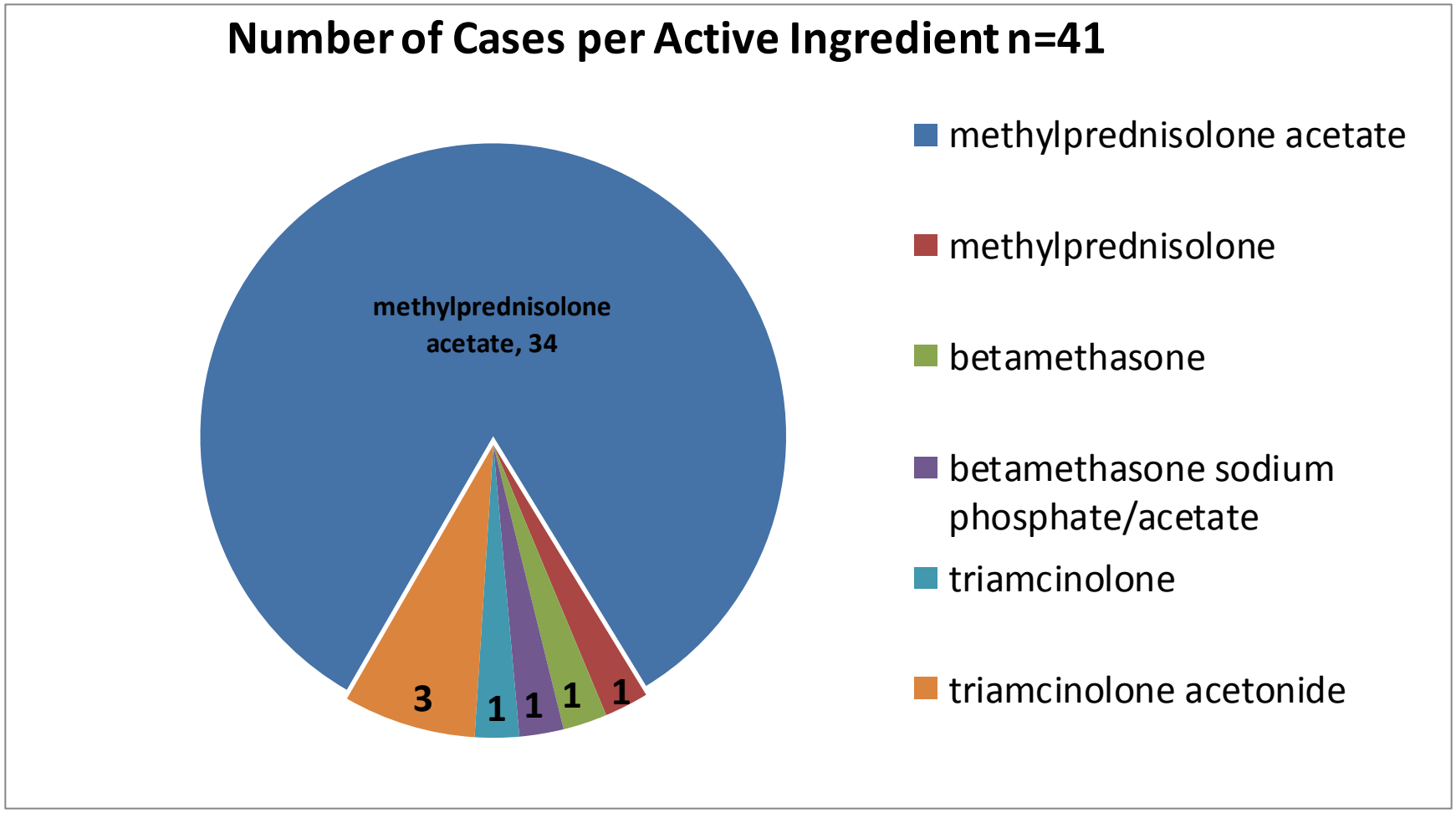
- 35-year-old female
- ^{4}prior caudal ESIs within 1 year
- **Methylprednisolone acetate** (dose unknown, suspension)
- Bupivacaine was also injected (route unknown)
- **One month: bowel and bladder dysfunction, peripheral sight problems and memory impairment**
- Events continued at the time of reporting

Nervous System Disorders FAERS Conclusion

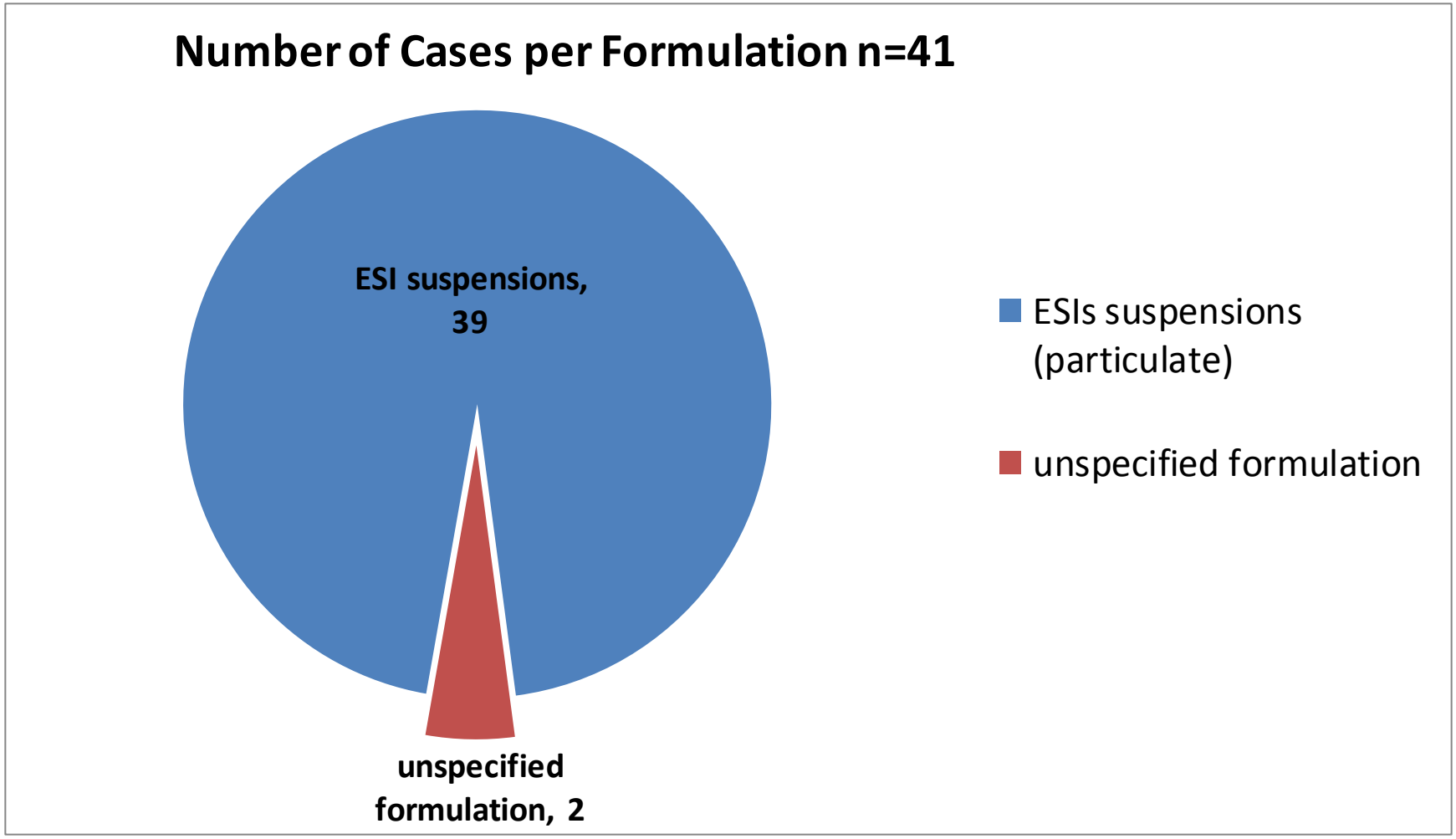
- Neurologic events occurred with wide variety of indications
  - most common: unspecified back pain
- Broad set of neurologic events reported
  - Most common: spinal cord infarction and paralysis
- Serious events occurred with a variety of active ingredients
  - most common: methylprednisolone acetate
- Serious outcomes occurred with all formulations and administration methods including fluoroscopy guided administrations

FAERS Overview of Spontaneous Reports of ESI and Arachnoiditis

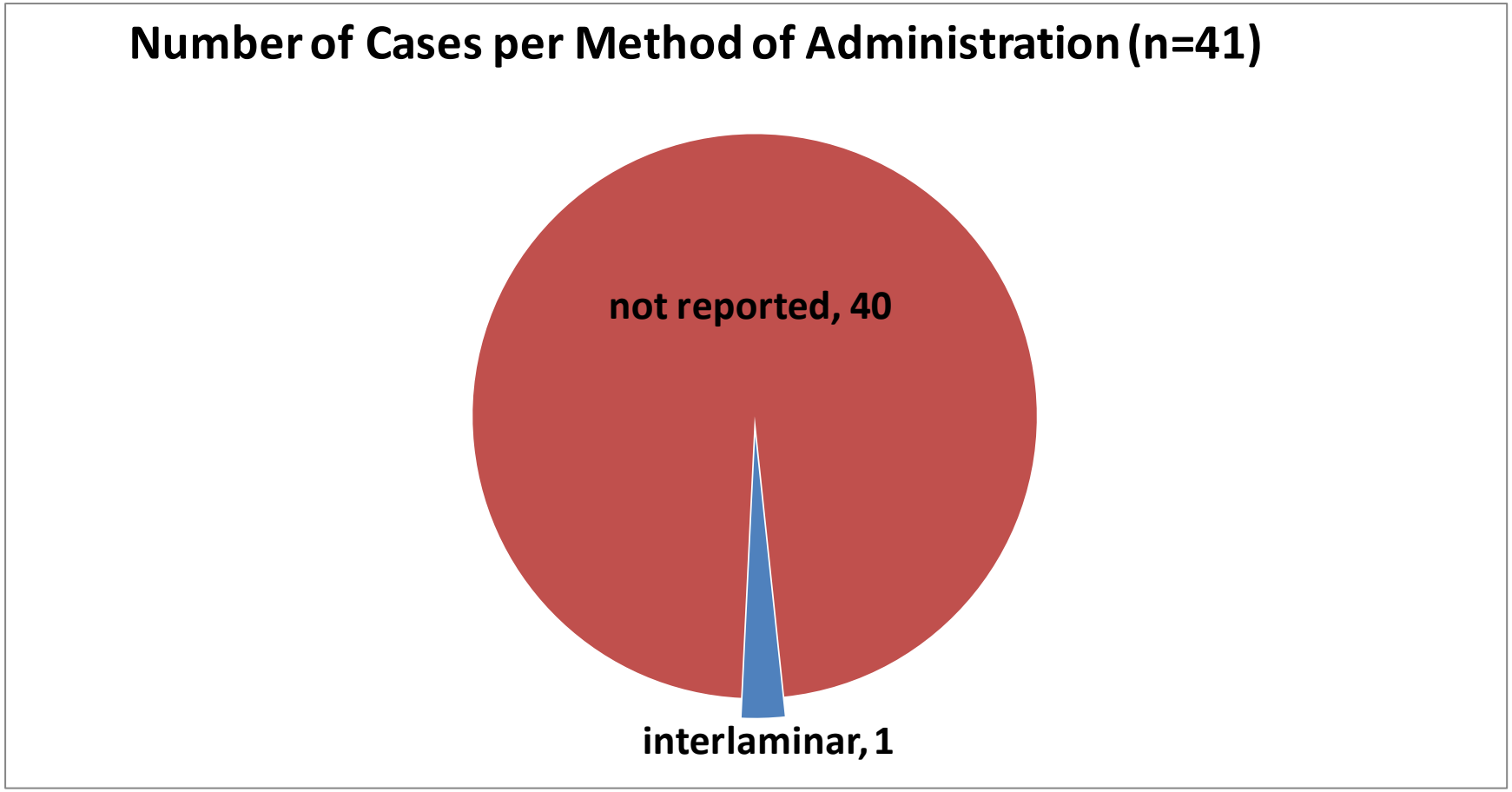
ESI Arachnoiditis Cases



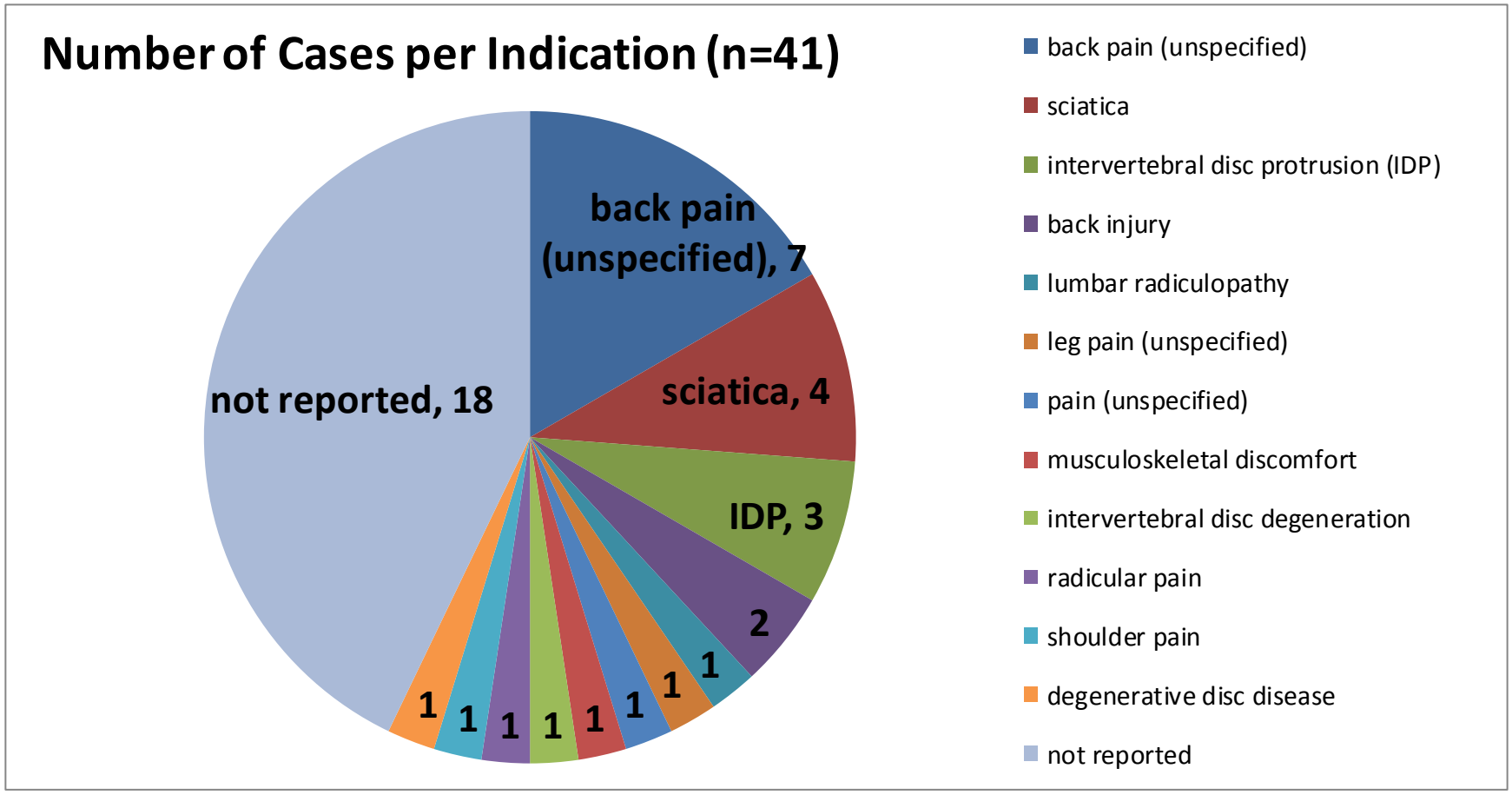
ESI Arachnoiditis Cases



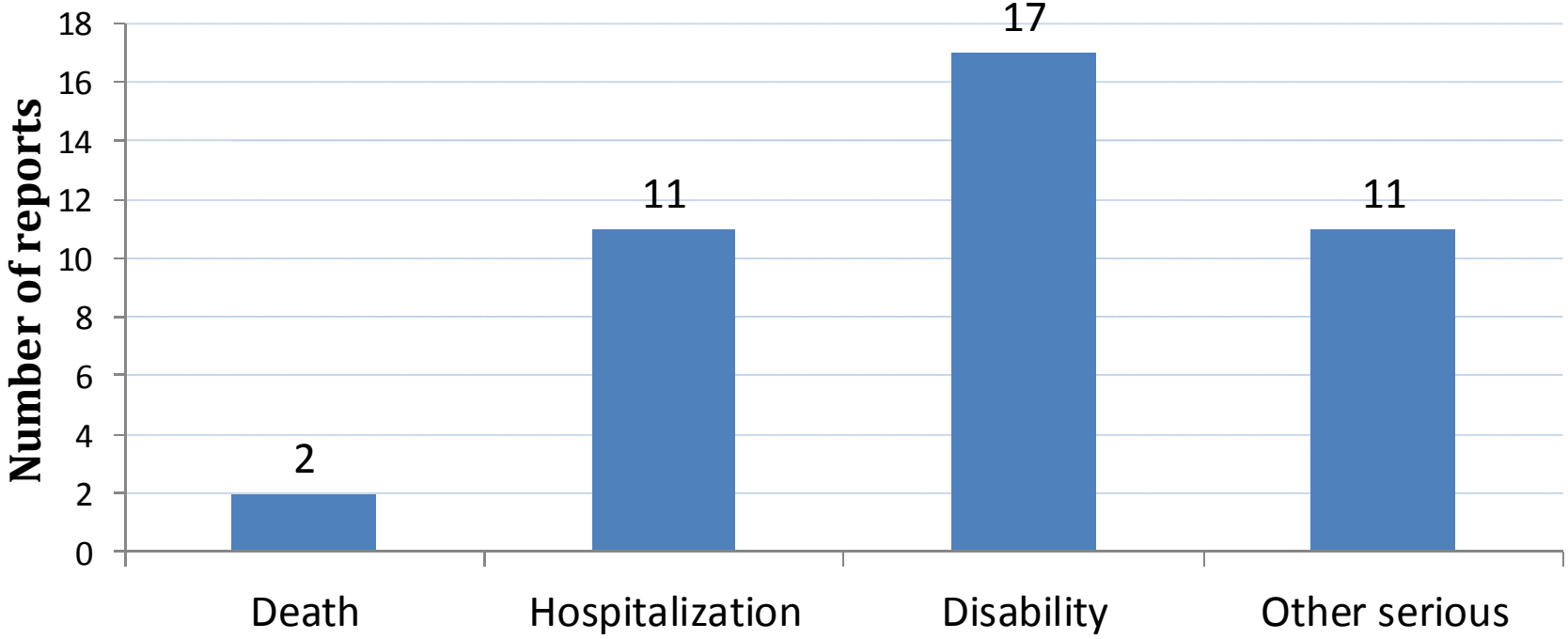
ESI Arachnoiditis Cases



ESI Arachnoiditis Cases



ESI Arachnoiditis Cases



^Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

Other Characteristics for ESI Arachnoiditis Cases (n=41)

- Prior ESIs (16)
- Concomitant anesthetics
  - bupivacaine (5), lidocaine (1)
- Concomitant contrast dye/imaging
  - Contrast media (1); no imaging (2)
- Time to onset of event
  - Within 1 day (3), 1 day – 1 month (5), >1 month (3)
- Reported possible etiologies for arachnoiditis
  - Unintentional/suspected intrathecal (4), prior recent intrathecal injection (1)

Examples of FAERS Cases of Arachnoiditis

- Female patient (age unknown) developed **adhesive arachnoiditis** (unknown time) after receiving two **methylprednisolone acetate** lumbar ESIs (1 week apart). The outcome of the event was reported as " totally disabled".
- A 43-year-old female consumer reported "Kenalog (**triamcinolone acetonide**), preservative, anesthetic, and dye caused toxic damage to nerve roots. Resulting diagnosis: **probable arachnoiditis, adhesive arachnoiditis.**" No further details provided.
- A35-year old female patient experienced **adhesive arachnoiditis** after receiving **betamethasone** (formulation and dose unknown). Two weeks later, the patient experienced "burning back pain … buzzing in legs and feet and severe stabbing and shooting pains." The outcome of the events were not reported.

FAERS Arachnoiditis Conclusion

- Events occurred in wide variety of indications
  - Most common: unspecified back pain
- Almost all cases reported ESI suspension
  - Most common: methylprednisolone acetate
  - No reports with ESI solution formulation
- One case reported method of administration
- Cases lacked clinical detail

Acknowledgments

- Tara Argual, PharmD
- Allen Brinker, M.D.
- Sara Camilli, PharmD
- Jane Gilbert, M.D. PhD
- Scott Proestel, M.D.

Overview of the Published Medical Literature

Jane L. Gilbert, MD, PhD
CDER|OSE|OPE|Division of Pharmacovigilance I
November 24, 2014

Objective of Literature Review

- Overview of the published medical literature
- Articles
  - Peer-review
  - Society journals
  - Frequently cited
- Goal is to convey scope, quality and nature of data and discussion in the literature

Literature Presentation Overview

- Search strategy and summary of results
- Transforaminal, interlaminar, cervical, lumbar: cases
- Hypothesized mechanism(s) of injury
- Perspectives on risk
- Key variables
  - Particulate/non-particulate (suspension/solution)
  - Method of administration
  - Imaging
  - Other procedural variables
- Conclusion

Search Strategy & Results, Serious Neurologic Events

- PubMed
  - Search terms: epidural, steroid, adverse, infarct, stroke, paralysis, transforaminal, interlaminar, caudal
  - Years: 8/1/2012– 8/1/2014
  - Approximately 200 articles retrieved
    - Case reports, trials, studies, literature reviews
    - Additional articles added as review progressed
    - Excluded: infections, reports of other confounders (e.g. spinal cord tumor), and others clearly not applicable
  - Annotated bibliography:
    - 35 articles
    - Published Case Reports (10), Review Articles (9), Studies (14), Other (6)

Search Strategy & Results, Arachnoiditis

- PubMed, October, 2014
  - Search terms: epidural steroid injections, arachnoiditis
  - Years: no restrictions
  - Results:
    - 20 articles retrieved
    - 1 describes arachnoiditis after caudal epidural
    - Others – uninformative

Literature Cases

- Similar to cases in FAERS; much diversity
  - Cervical Transforaminal (TF)
  - Cervical Interlaminar (IL)
  - Lumbar TF
  - Lumbar IL
  - With fluoroscopy/CT/digital subtraction angiography (DSA)

Diverse Cases

Author	Location	TF /IL	Steroid	Outcome (date last reported)
Tiso	Cervical	TF	TAC	Cerebellar Infarct ; death
Cohen-Adad	Cervical	IL	MPA	Left hemiparesis and sensory loss (28 mos); intramedullary injection
Houten	Lumbar	TF	MPA	Numbness + paralysis of lower extremities (8 mos)
Houten	Lumbar	TF	"BTN"	Paraparesis with L1 level; strength improved from 3/5 to 4/5 (1 month)
Thefenne	Lumbar	IL	PA	Paraplegia; some recovery: can walk 200 m, "continues with urinary and sensory disorders" (4 mos); MRI=> embolization

TAC=triamcinolone, MPA =methylprednisolone acetate, PA = prednisolone acetate, BTN =Betamethasone

Proposed Mechanisms of Injury

- Hypothesized cause of injury
  - Often unknown
  - Intra-arterial/intrathecal/intradiscal/intramedullary
  - Spinal cord or brainstem infarct (from embolization or vascular spasm)
  - Epidural hematoma
  - Brainstem hemorrhage
- Result
  - Severe spinal cord injury, weakness, paralysis, bowel and bladder dysfunction, death

Most Common Hypothesis for Mechanism of Injury

Inadvertent intravascular injection with a particulate steroid product leads to an embolic event → spinal cord infarct

Candido et al. Cervical epidural steroid injections for the treatment of cervical spinal (neck) pain. Curr Pain Headache Rep. 2013.

Proximity of Vertebral Artery

Fitzgerald, Vertebral artery position in the setting of cervical degenerative disease: implications for selective cervical transforaminal epidural injections. Interv Neuroradiol. 2013.

In an effort to assess the position of the vertebral artery relative to a typical TF injection, the authors assess cervical TF injections in 68 patients/70 injections. They contend that the "needle trajectory intersected with the vertebral artery in 30 of 70 injections by CT fluoroscopy."

Limitation: no information about how patients were selected or how representative they are of the general population

Frequency of an Intravascular Injection

Author	# Patients /#Injections	Injection Type	% Intravascular
Furman (2000)	670/761	TF Lumbar	11.2% *
Furman (2003)	337/504	TF Cervical	19.4%
Hong (2013)	219/251	TF Lumbar	15.5%

Limitations: All 3 single center studies with unknown generalizability

*Intravascular injection was higher at S1 (21.3%) than at lumbar levels (8.1%)

Perspectives on Risk

McGrath et al. Incidence and characteristics of complications from epidural steroid injections. Pain Med 2011.

- Retrospective chart review over 7-year period
- 4265 injections/1857 patients
- Cervical IL (161), Lumbar IL (123), Lumbar TF(3964), Caudal (17)
- No major complications identified

- *Limitations: Single center study, may not be generalizeable. Use of electronic medical records to identify those who initiated medical contact after ESI may have missed adverse events.*

Perspectives on Risk

Waldman. Complications of cervical epidural nerve blocks with steroids: a prospective study of 790 consecutive blocks. Reg Anesth. 1989.

- 215 patients/790 cervical blocks
- Followed for 6 weeks
- 2 dural punctures (requiring blood patch)
- 3vasovagal syncope
- One superficial infection at wound site
- No other important sequelae

- *Limitations: Single center study, may not be generalizeable*.

Variables of Interest

- Particulate vs Non-Particulate
- Methods of Administration
- Imaging
- Other procedural
  - Sedation
  - Test Dose
  - Type of Needle

Particulate vs Non-Particulate: Animal Data

Okubadejo et al. Perils of Intravascular Methylprednisolone Injection into the Vertebral Artery. J BoneJoint Surg Am. 2008.

- 11 pigs: vertebral artery injections
- 4 particulates (methylprednisolone acetate)
- 7 non-particulates (dexamethasone sodium phosphate and prednisolone sodium succinate)
- 4 receiving particulates expired; 7 receiving non-particulates recovered

- *Limitation: animal study and small.*

Particulate vs Non-Particulate: Human Data

- The clinically significant and catastrophic neurologic events presented in cases in the literature were all associated with particulate steroids. Of the 8 cases providing information about the type of steroid used, 7 cases were associated with particulates and 1 was uncertain.

Cautionary note: It is not possible to say whether these data reflect differences in safety or differences in drug use.

Method of Administration: Transforaminal vs Interlaminar vs Caudal

- *Consensus view*: Transforaminal (TF) injections are more risky than the others

- Ghai: "Catastrophic complications reported with the TF approach have raised concerns regarding its use."

Ghai et al. Transforaminal versus parasagittal interlaminar epidural steroid injection in low back pain: a randomized, double-blind, active-control trial. Pain Physician. 2014.

Method of Administration: Evidence

- More reports of clinically serious neurological events with transforaminal than with other approaches
- 10 cases from the literature
  - 6transforaminal
  - 2 interlaminar
  - 1 caudal
  - 1unknown

Cautionary note: It is not possible to say whether these data reflect differences in safety or differences in the usage of these various methods.

Intravascular Injection: Transforaminal vs Interlaminar vs Caudal

Sullivan. Incidence of Intravascular uptake in lumbar spinal injection procedures. Spine. 1976.

- 15 physicians at 7 outpatient spine centers across the U.S. recorded data about intravascular uptake during 1219 contrast-enhanced fluoroscopically-guided lumbar spinal injections
  - Overall incidence of intravascular uptake = 8.5%
  - Caudal route = 10.9%
  - Transforaminal = 10.8%
  - Interlaminar = 1.9%

Limitations: Older study, outpatient setting. Incidence for transforaminal injections consistent with others; no other estimate for interlaminar injections

Imaging

- Fluoroscopy, with and without contrast
- CT guidance
- Digital subtraction angiography – for identification of vascular compromise during injection
  - 80 yo male, interlaminar injections previously, *now transforaminal*
  - DSA performed twice to insure no intravascular contrast spread
  - Test dose of lidocaine
  - Then triamcinolone acetonide →weakness, numbness, paraplegia from spinal cord infarction
  - Discharged with LE paralysis, incontinence of bowel and bladder
- ***Chang Chien et al. Digital subtraction angiography does not reliably prevent paraplegia associated with lumbar transforaminal epidural steroid injection. Pain Physician. 2012.***

Other Procedural Variables Discussed in the Literature

- *Sedation*: an awake patient can experience pain and alert injectionist to improper placement of needle
  - *Tiso: patient remained "conscious" yet still experienced a cerebellar infarct and died*
- *Local anesthetic test dose*: administration of a test dose may help determine correct location of needle
  - *Chang Chien: patient had a test dose yet still experienced spinal injury and paraplegia*
- *Blunt needle*: a blunt needle may prevent vascular penetration
  - *Ilkhchoui and Koshkin: patient experienced vascular penetration with a blunt curved needle*

Arachnoiditis

Nanjayan et al. Arachnoiditis following caudal epidural injections for the lumbo-sacral radicular pain. Asian Spine J. 2013.

- 58 yo male, 2 caudal ESIs with triamcinolone, for left sided sciatica secondary to disc protrusion (L3/L4)
- 4 days after 2nd injection → new onset right sided sciatica
- Increased inflammatory markers (CRP, WBC); signs of sepsis
- Treated with antibiotics for 4 weeks
- Gradually improved but remained with left foot drop
- Likely infectious etiology

Arachnoiditis

Abram and O'Connor, Complications associated with epidural steroid injections. Reg Anesth. 1996.

- "Several cases of aseptic meningitis, arachnoiditis, and bacterial meningitis…have been reported after subarachnoid steroid injections."
- No other references to specific cases of arachnoiditis

Literature Conclusion

- No large trials dedicated to assessing safety
- Significant neurologic adverse events, some catastrophic and irreversible can occur with ESI use. Though apparently uncommon, the exact incidence is unknown.
- No catastrophic cases with what are commonly referred to as non-particulates (solutions); unclear whether due to variations in safety or to lower use
- Significant neurologic adverse events reported with all methods of administration, with numerous procedural variations, including a variety of imaging techniques

Additional References

- Abram and O'Connor. Complications associated with epidural steroid injections. Reg Anesth. 1996.
- Furman et al. Incidence of Intravascular Penetration in Transforaminal Lumbosacral Epidural Steroid Injections. Spine. 2000.
- Furman et al. Incidence of Intravascular Penetration in Transforaminal Cervical Epidural Steroid Injections. Spine. 2003.
- Houten and Errico. Paraplegia after lumbosacral nerve root block: report of three cases. The Spine Jn. 2002.
- McGrath et al. Incidence and Characteristics of Complications from Epidural Steroid Injections. Pain Medicine. 2011.
- Nelson, DA. Dangers from methylprednisolone acetate therapy by intraspinal injection. Arch Neurol. 1988.
- Sullivan et al. Incidence of intravascular uptake in lumbar spinal injection procedures. Spine. 2000.
- Thefenne et al. A rare case of paraplegia complicating a lumbar epidural infiltration. Annals of Physical and Rehabilitation Medicine. 2010.
- Waldman SD. Complications of cervical epidural nerve blocks with steroids: a prospective study of 790 consecutive blocks. Reg Anesth. 1989.
- Windsor et al. Cervical Transforaminal Injection: Review of the Literature, Complications, and a Suggested Technique. Pain Physician. 2003

Drug Utilization Patterns for Epidural Steroid Injections (ESIs) 2009-2013

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Office of Surveillance and Epidemiology
FDA/CDER

Anesthetic and Analgesic Drug Products Advisory Committee Meeting
November 24, 2014

Outline

- Methods
- Study Patient Population
  - ≥65 years old: CMS Medicare (Part A and B)
  - <65 years old patients- IMS Data Nationally Projected to the Commercially Insured U.S. Population
- Key Findings
- Limitations
- Conclusion

Methods: Patient Selection

- Presence of claims for CPT* code for epidural injection and HCPCS** code indicating steroid use
  - within 2 days of each other for Medicare population
  - on the same day for commercially insured population

*CPT: Current Procedural Terminology
**HCPCS: Healthcare Common Procedure Coding System

Methods:
Method of Epidural Injection Administration

- Transforaminal epidural injection CPT codes

  64479, 64480, 64483, and 64484

- Interlaminar and caudal epidural methods of epidural injection CPT codes

  62289, 62310, 62311, 62318, and 62319

Methods: HCPCS Codes by Steroid

HCPCS codes for Injectable Steroid Administration by Formulation

Suspension
J0702 INJ BETAMETHASONE ACETATE & PHOSPHATE 3 MG
J1020 INJECTION METHYLPREDNISOLONE ACETATE 20 MG
J1030 INJECTION METHYLPREDNISOLONE ACETATE 40 MG
J1040 INJECTION METHYLPREDNISOLONE ACETATE 80 MG
J1094 INJECTION DEXAMETHASONE ACETATE 1 MG
J1700 INJECTION HYDROCORTISONE ACETATE UP TO 25 MG
J2650 INJECTION PREDNISOLONE ACETATE UP TO 1 ML
J3300 INJ TRIAMCINOLONE ACETONIDE PRES FREE 1 MG
J3301 INJECTION TRIAMCINOLONE ACETONIDE NOS 10 MG
J3302 INJECTION TRIAMCINOLONE DIACETATE PER 5 MG
J3303 INJECTION TRIAMCINOLONE HEXACETONIDE PER 5 MG
Solution
J0704 INJECTION BETAMETHASONE SODIUM PHOSPHATE-4 MG
J1100 INJECTION DEXAMETHOSONE SODIUM PHOSPHATE 1 MG
J1710 INJ HYDROCORTISONE SODIUM PHOSPHATE TO 50 MG
J1720 INJ HYDROCORTISONE SODIUM SUCCINATE TO 100 MG
J2640 INJ PREDNISOLONE SODIUM PHOSPHATE TO 20 MG
J2920 INJ METHYLPRDNISOLONE SODIUM SUCCNAT TO 40 MG
J2930 INJ METHYLPRDNISOLONE SODIUM SUCCNAT TO 125 MG

≥65 years:

- **Medicare Population**

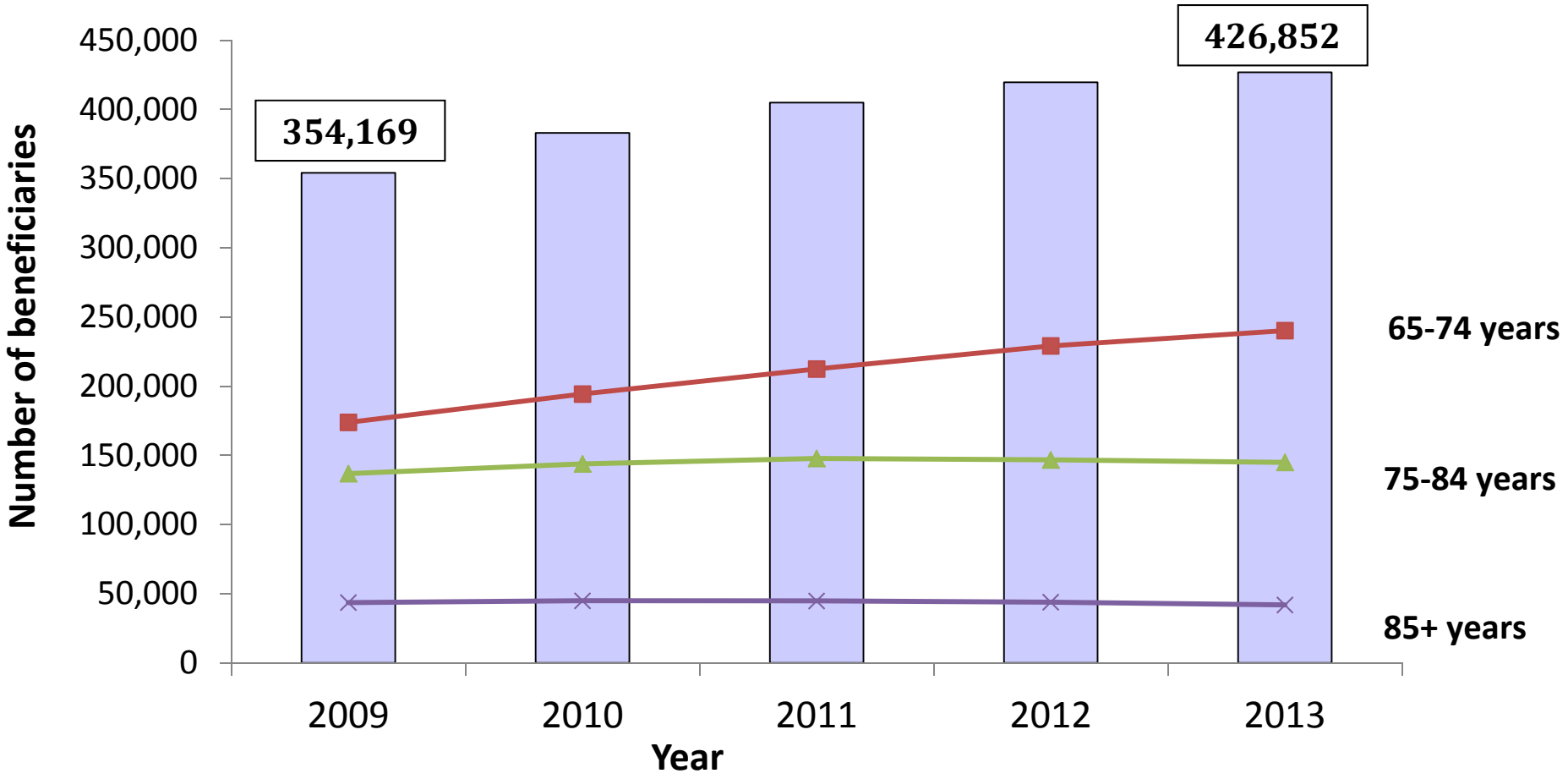
≥65 years: Data Source

CMS Database:

- Time period: 2009-2013
- Included beneficiaries aged ≥65 years
- Same HCPCS and CPT Codes
  - ESI event defined as epidural injection code and steroid injection code within 2 days
  - Required enrollment in Medicare Parts A & B

Patients: ≥65 years

Number* of Medicare Part A&B beneficiaries (patients) receiving ESIs, by age



**Not nationally estimated or nationally representative of the US 65+ population*

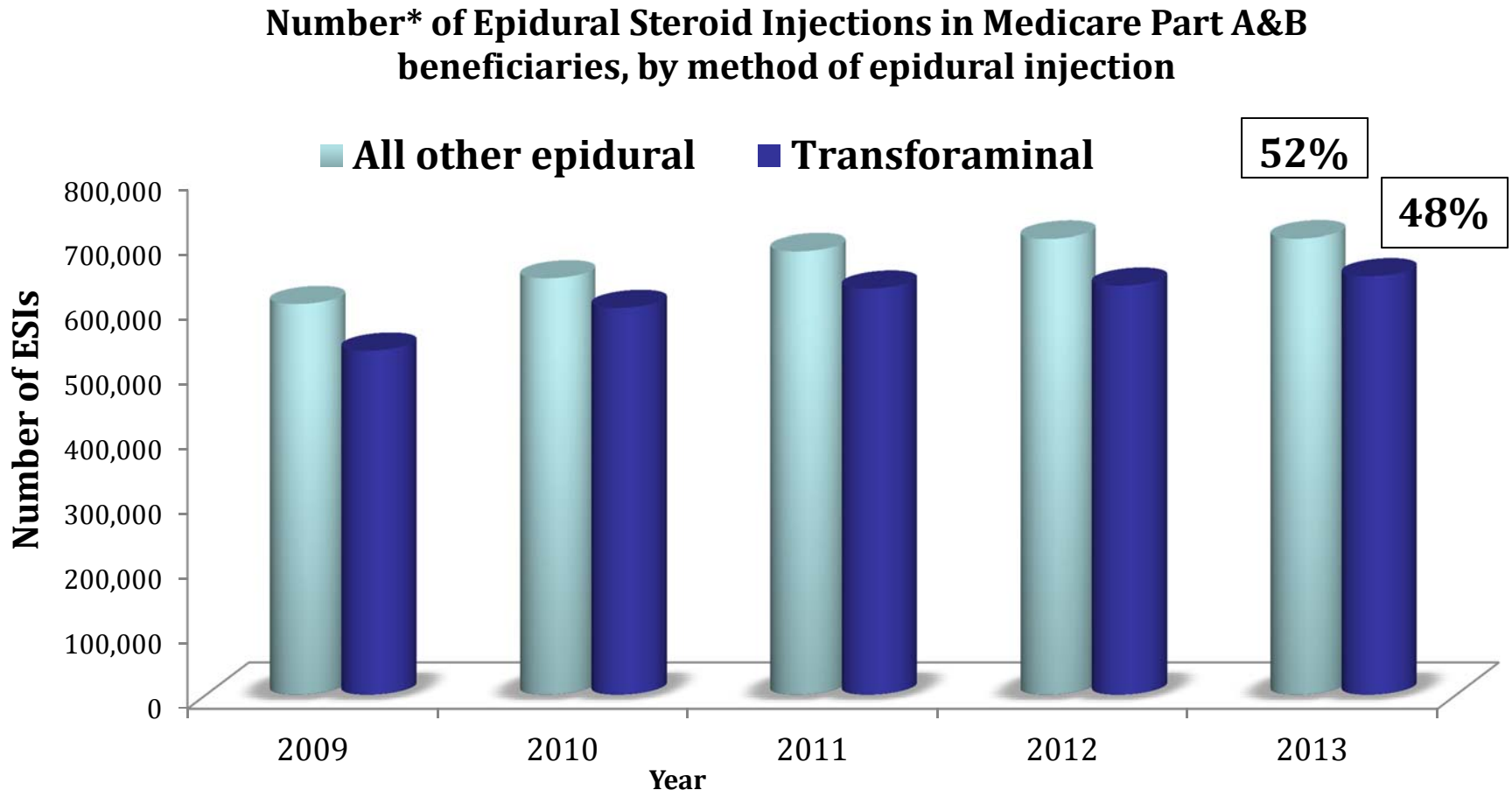
Total Patients and ESIs: ≥65 years

Total Number of Beneficiaries (Unique Patients) and Total Number of ESIs in Medicare population, by year

	2009	2010	2011	2012	2013
Number of Beneficiaries*	354,169	382,990	404,926	419,621	426,852
Number of ESIs	1,134,747	1,241,844	1,313,145	1,336,768	1,351,844

*beneficiaries could be included across multiple years

Number of ESIs by Method of Administration: ≥65 years old

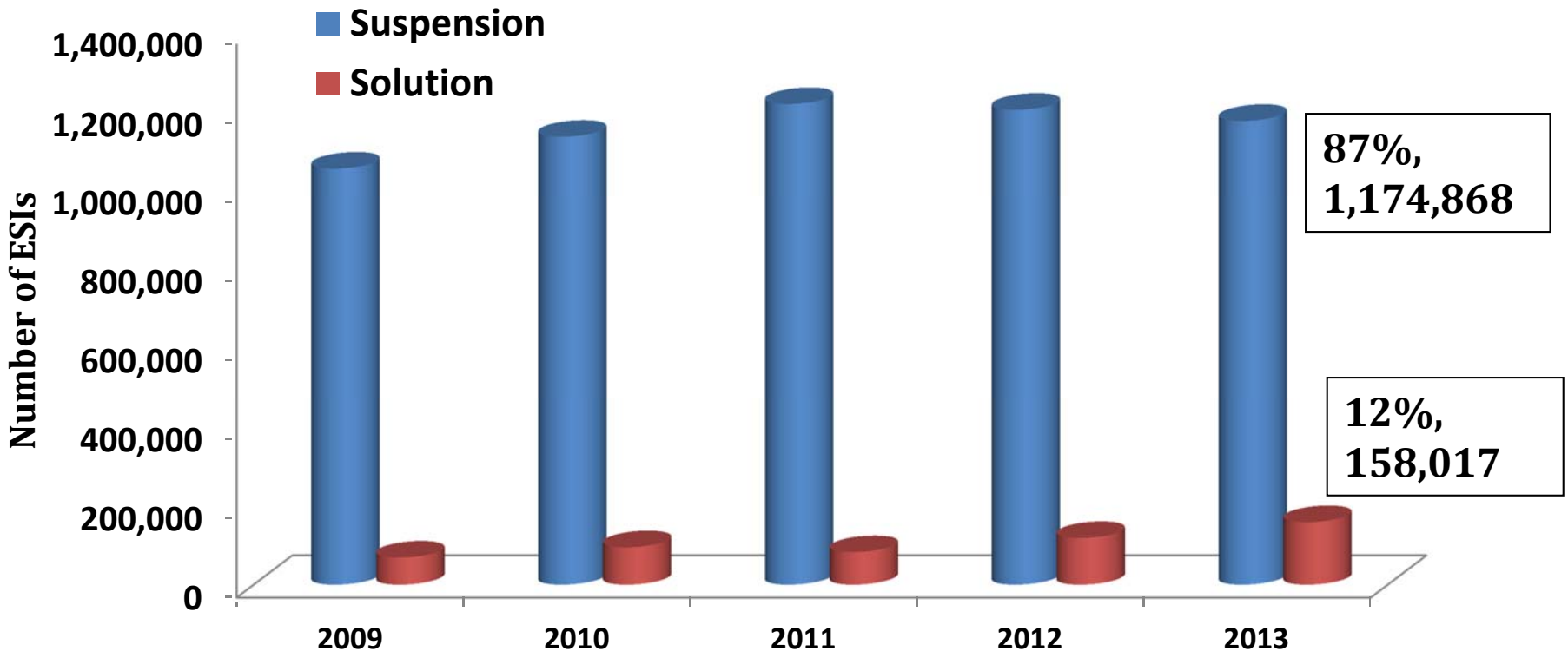


All other epidural methods include interlaminar and caudal

**Not nationally estimated or nationally representative of the US ≥65 population*

Number of ESIs by Formulation: ≥65 years old

Number* of Epidural Steroid Injections in Medicare Part A&B, by steroid formulation**

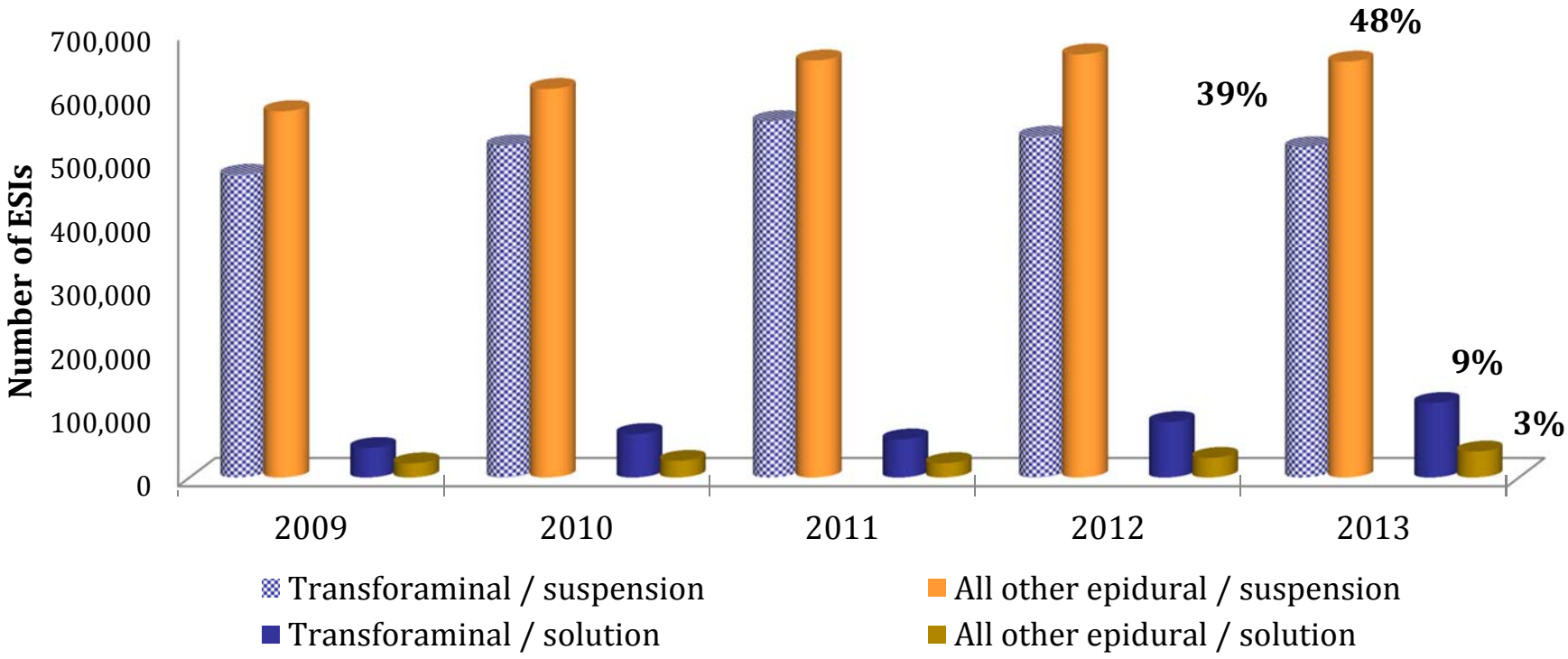


**Not nationally estimated or nationally representative of the US ≥65 population*

***Less than 1.5% of injections had both a solution and suspension code*

Number of ESIs by Method of Administration and Formulation: ≥65 years

Number* of Epidural Steroid Injections in Medicare Parts A&B by method of epidural injection and steroid formulation**



All other epidural methods include interlaminar and caudal

**Not nationally estimated or nationally representative of the US ≥65 population*

***Less than 1.5% of injections had both a solution and suspension code*

<65 years:

- **IMS LifeLink™ Data Nationally Projected to the Commercially Insured U.S. Population**

<65 years: Data Source

IMS LifeLink™ Health Plan Claims Database:

- Time period: 2009-2013
- Included patients aged <65 years
- Study base population includes 101 health insurance plans
  - 66 million covered lives
- Captures all prescription, procedure, medical claims data
- Data *are* nationally projected to the commercially insured U.S. population

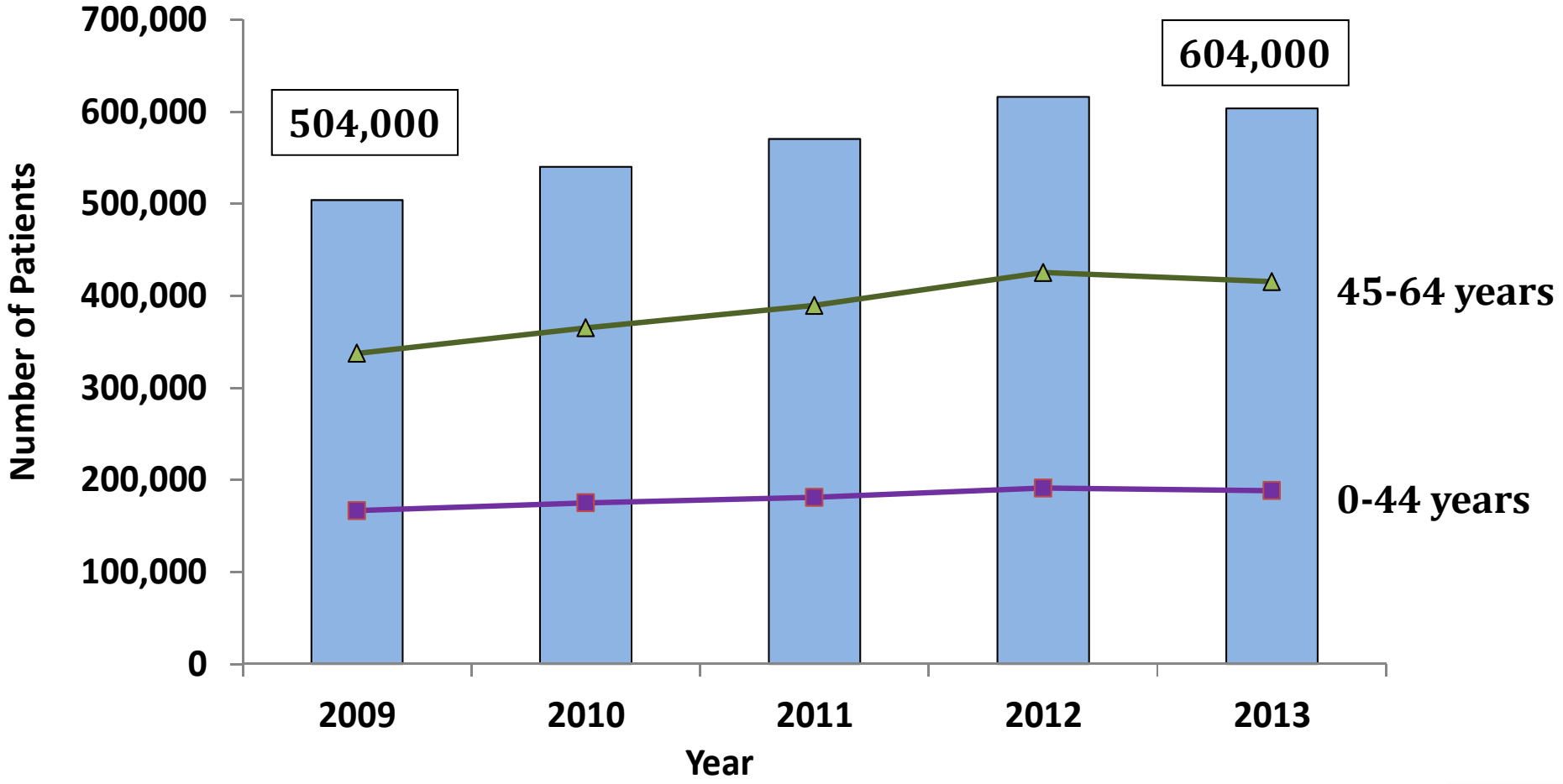
Results: Commercially Insured Patients <65 years

- Unique patients receiving ESIs
- 52% of patients had more than one injection during the year
- On average patients had ~ 2 injections per year

Source: IMS, Lifelink™ Health Plan Claims Database. Y2009-2013. Extracted October 2014

Unique Patients: <65 years

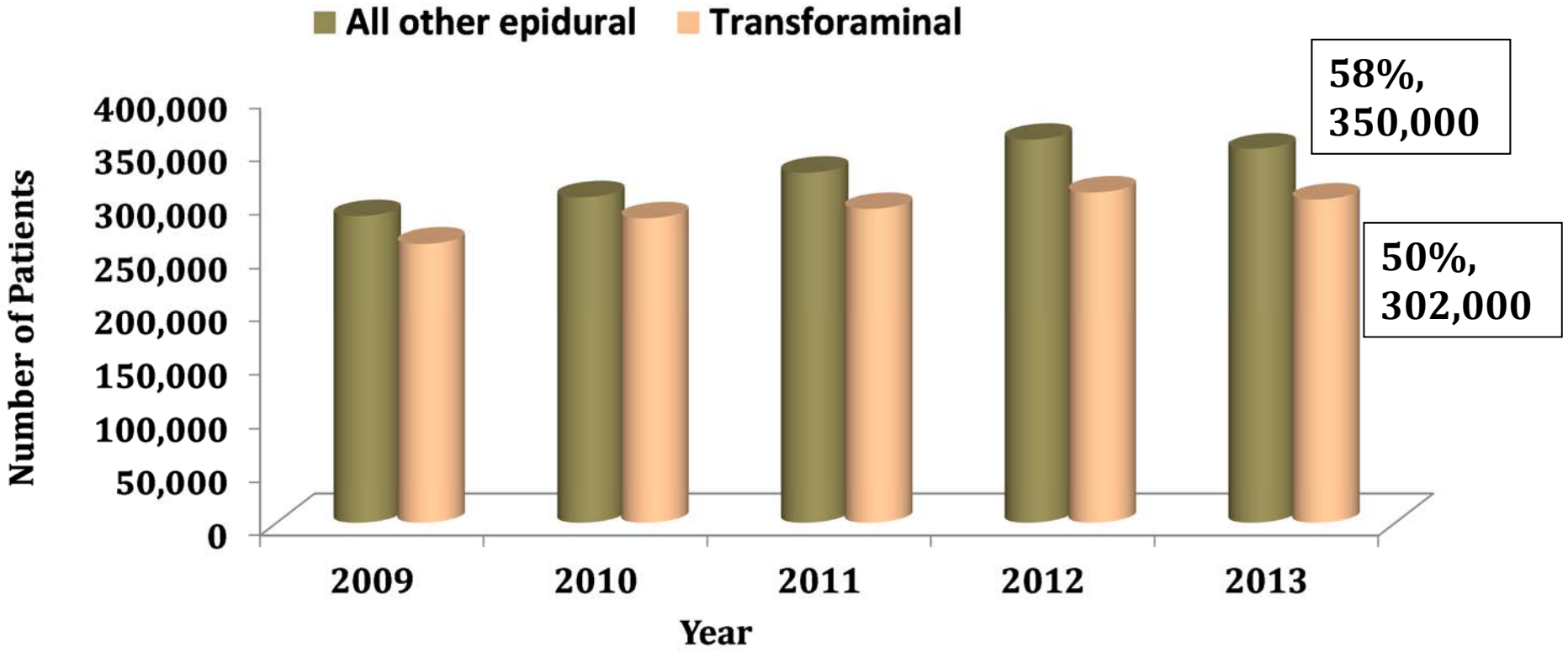
Nationally estimated number of unique patients aged <65 years receiving ESIs in the commercially insured U.S. population, stratified by patient age



Source: IMS, Lifelink™ Health Plan Claims Database. Y2009-2013. Extracted October 2014

Patients by Method of Administration: <65 years

Nationally estimated number of patients receiving ESIs in the commercially insured U.S. population, by transforaminal and all other epidural methods* of administration**

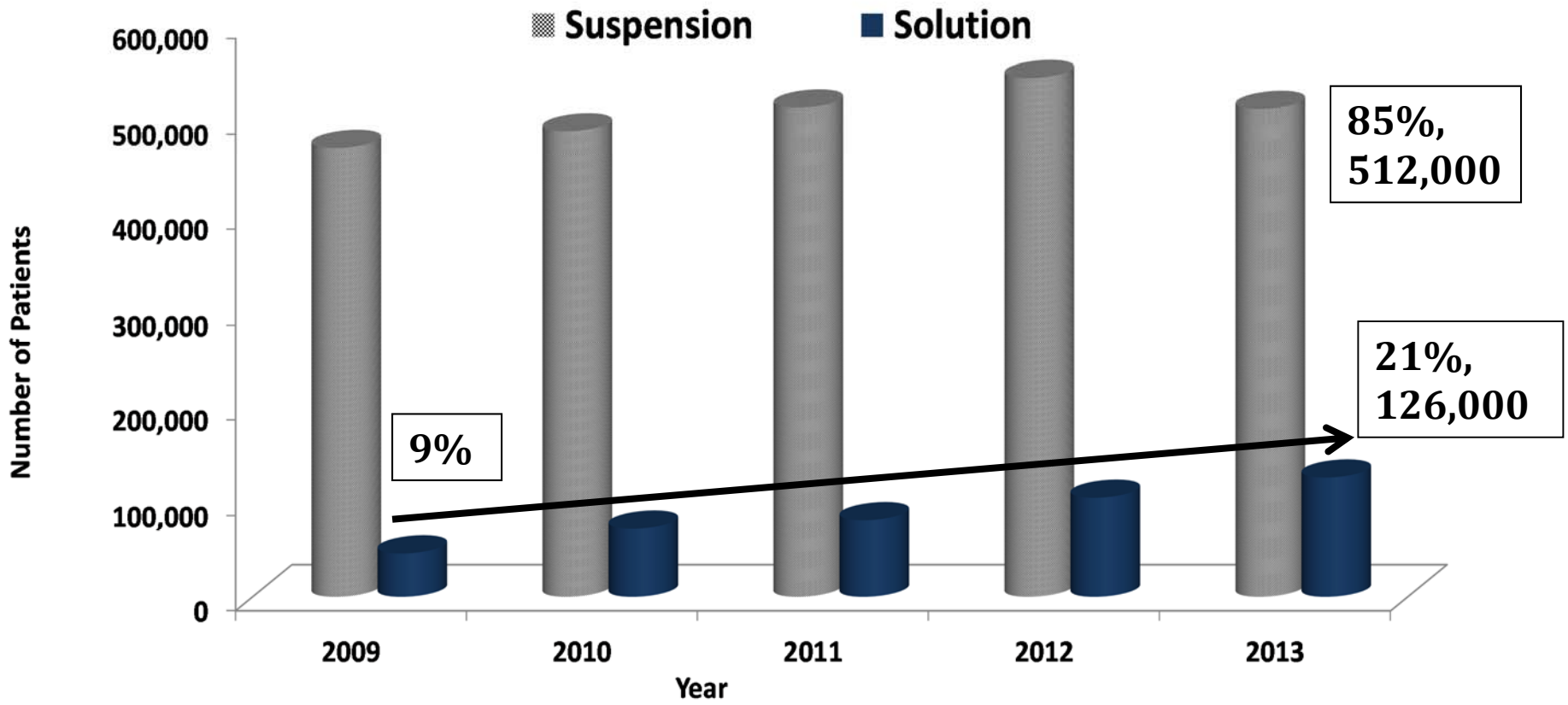


*All other epidural methods include interlaminar and caudal
** Patients had both epidural method types in the same year about 8.7% of the time

Source: IMS, Lifelink™ Health Plan Claims Database. Y2009-2013. Extracted October 2014

Patients by Steroid Formulation: <65 years

Nationally estimated number of patients receiving ESIs in the commercially insured U.S. population, by type of steroid formulation*

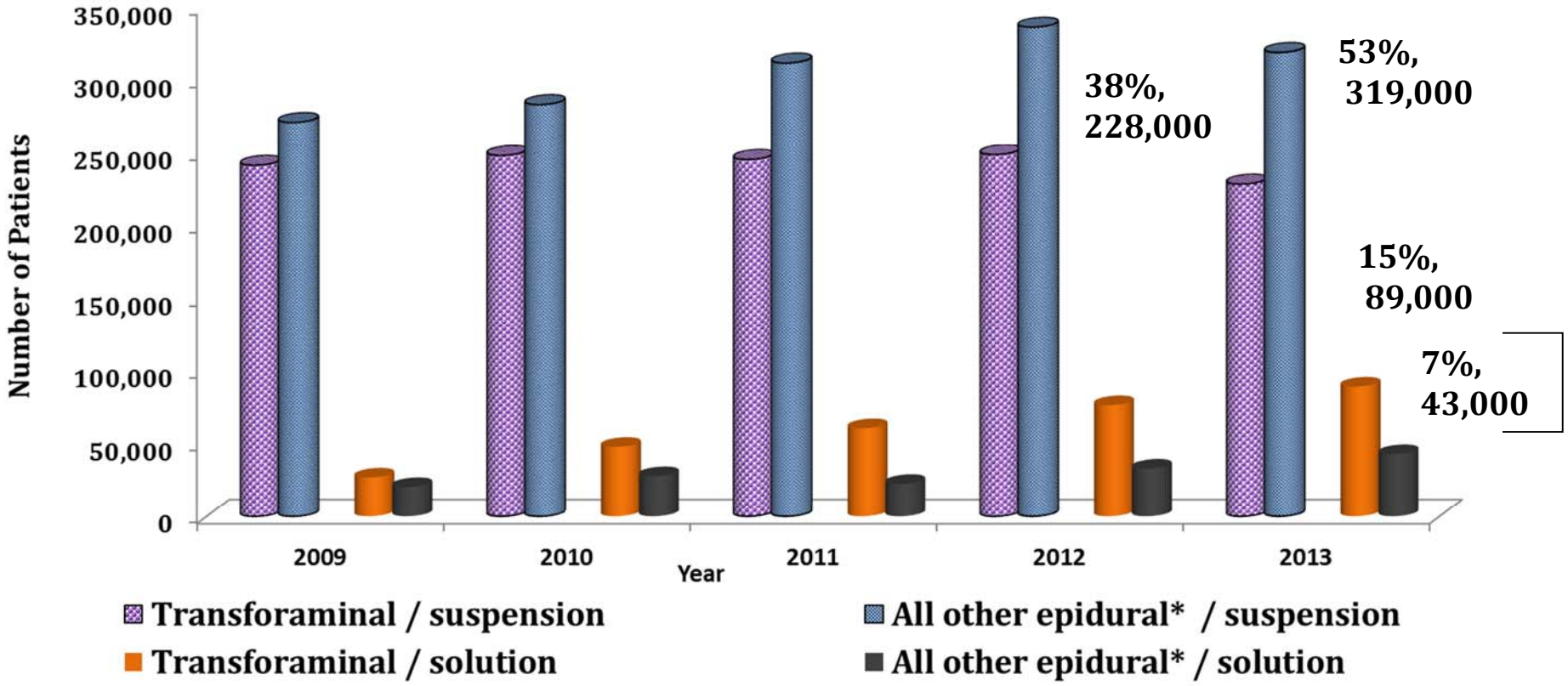


*Patients had both steroid formulation types in the same year about 4.3% of the time

Source: IMS, Lifelink™ Health Plan Claims Database. Y2009-2013. Extracted November 2014

Patients by Method of Administration and Steroid Formulation: <65 years

Nationally estimated number of patients receiving ESIs in the commercially insured U.S. population, by method of epidural administration and steroid formulation**



*All other epidural methods include interlaminar, and caudal.
**Unique patient subtotals may not sum exactly due to possible double counting of patients who received different treatments over time

Source: IMS, Lifelink™ Health Plan Claims Database. Y2009-2013. Extracted November 2014

Key Findings

- Increase in number of patients receiving ESI over 2009-2013
  - Medicare (≥ 65 years): 427,000 patients in 2013
  - Commercially insured (<65 years): 604,000 patients in 2013
- Transforaminal Vs Other Methods of Epidural Injection
  - Medicare (≥ 65 years): 48% transforaminal
  - Commercially insured (<65 years): 50% transforaminal
- Steroid formulation
  - Medicare (≥ 65 years): 87% suspension
  - Commercially insured (<65 years): 85% suspension
- Transforaminal / suspension
  - Medicare (≥ 65 years): 39%
  - Commercially insured (<65 years): 38%
- Transforaminal / solution use increased
  - Medicare (≥ 65 years): 4% to 9%
  - Commercially insured (<65 years): 5% to 15%

Limitations

- Medicare (≥65 years):
  - Does not represent the entire ≥65 population of the U.S.
    - Includes all Medicare Part A and B
    - Does not include cash and commercially insured, etc.
  - Available data do not allow further breakdown of non-transforaminal epidural route into interlaminar or caudal.

Limitations

- Commercially insured (<65 years):
  - Data obtained from a *sample* of healthcare claims from insured U.S. population
  - Patient sample restricted to commercial or self insured
    - Does not include cash payers, Medicare, and Medicaid population
  - Claims data are collected for billing purposes; not clinical care
  - Available data does not allow further breakdown of non-transforaminal route into interlaminar or caudal.
  - Projected data on number of injections not yet available

Conclusions

ESI use in patients ≥65 and <65 years increased from 2009-2013

- Nearly half of epidural methods were transforaminal
- Majority of steroids were suspensions
  - Solution formulation utilization slightly increased
- Over 1/3rd of ESI use was steroid suspension by transforaminal epidural method
- Steroid solution use by transforaminal epidural method increased

Thank You

Safe Use Initiative

John Whyte, MD, MPH

Director

Professional Affairs and Stakeholder Engagement

FDA's *Safe Use Initiative*

Launched in 2009

Goal: Reduce preventable harm by identifying specific, preventable medication risks and developing, implementing and evaluating cross-sector interventions with partners who are committed to safe medication use

FDA's *Safe Use Initiative*

Safe Use Initiative accomplishes this through creating and facilitating public and private collaborations within the healthcare community

FDA's *Safe Use Initiative*

Safe Use Initiative's efforts are of non-regulatory nature but align with, complement and/or reinforce FDA's regulatory efforts

FDA's *Safe Use Initiative*

Potential partners in Safe Use include:

- Federal agencies
- Healthcare professionals and professional societies
- Pharmacies, hospitals, and other healthcare entities
- Patients, caregivers, consumers, and their representative organizations

Timeline – ESI'S

- 2009 Dr. James Rathmell reached out to the FDA with concerns regarding the safe use of ESI's
- The FDA initiated a safety review based on this initial inquiry
- 2011 *Safe Use Initiative* facilitated organization of an expert working group

Facilitation of Expert Panel

- Dr. Rathmell identified top experts in the field who have published on ESI
  - Pain experts, anesthesiologists and other experts, and members of professional societies
- SUI reached out to identified experts and invited them
- Panel members assumed the lead on the project distributing information and summarizing discussions

Working Group Goals

- Understand the causes of the neurologic injuries associated with ESI's and devise strategies to mitigate their risk
- Provide information to the health care community to reduce risk

Safe Use Staff Role

- Facilitate organization of expert Working Group
- Safe Use did not actively participate in the deliberations or decision-making process

Working Group

- Guidance from the Working Group prompted further discussion and voluntary input from national pain organizations
- The Working Group drafted clinical considerations for healthcare professionals
- Resulting work and outcomes are the intellectual property of collaborating stakeholders and are not endorsed by the FDA

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

Charge to the Committee

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research, FDA

November 24, 2014

ESI are Performed Frequently

- Our analysis of IMS data and CMS data indicate that ESI are performed frequently
- Any regulatory action related to ESI may have substantial intended and unintended consequences

Class Warning – July 2014 Corticosteroid Labeling

WARNING

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids (see **WARNINGS: Neurologic**). Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

Feedback from Professional Societies

- Most professional societies that provided feedback to FDA appreciated FDA's efforts on behalf of patient safety

HOWEVER…

- We were repeatedly told that we got the messaging wrong

Wrong in what way?

- Our warning was overly broad and did not point out important distinctions in safety among the types of ESI
  - Serious neurological adverse events only occur with "particulate" (suspension) corticosteroid formulations
  - Serious neurological adverse events only occur with injections administered by the transforaminal route
- ESI <u>have</u> been shown to be efficacious and safe

The Data In This Area are Limited

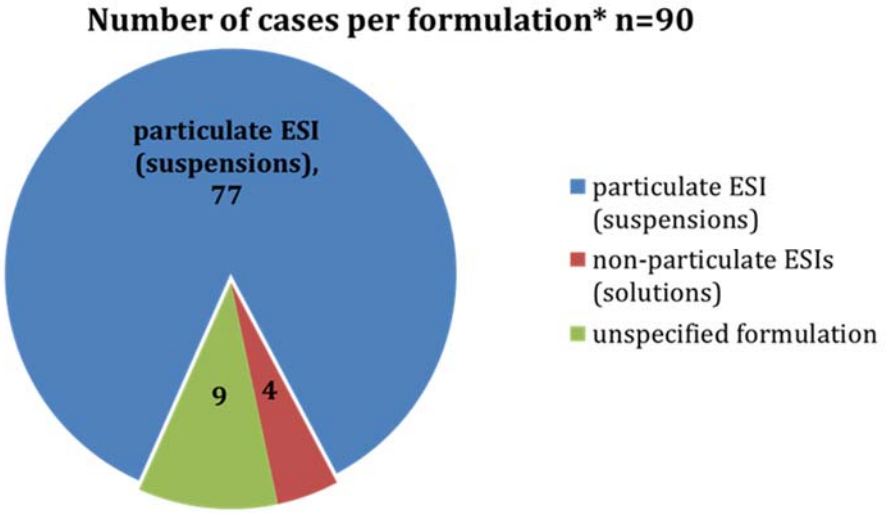
- Case reports (reported to FDA or in the medical literature), case series, and systematic literature reviews of case reports and case series define the extent of the safety data available
- Reports submitted to FDA vary in information provided
  - In the ESI evaluation, reports often lacked important information such as method of administration
- If the safety across the product class is the same, we would expect that the types of adverse event reports submitted to FDA or published in the literature would be
  - proportional to the frequency with which various corticosteroid products were administered;
  - proportional to the frequency with which various methods of administration are used;
  - however, we have no data to support this assumption

Reporting of Neurological FAERS Cases with Corticosteroid Suspensions Mirrors Use

Type of steroid formulation, 2013

- Commercially insured (<65 yrs): 85% suspension
- Medicare (≥ 65 ys): 87% suspension

ESI Formulations and Nervous System Disorder Adverse Events

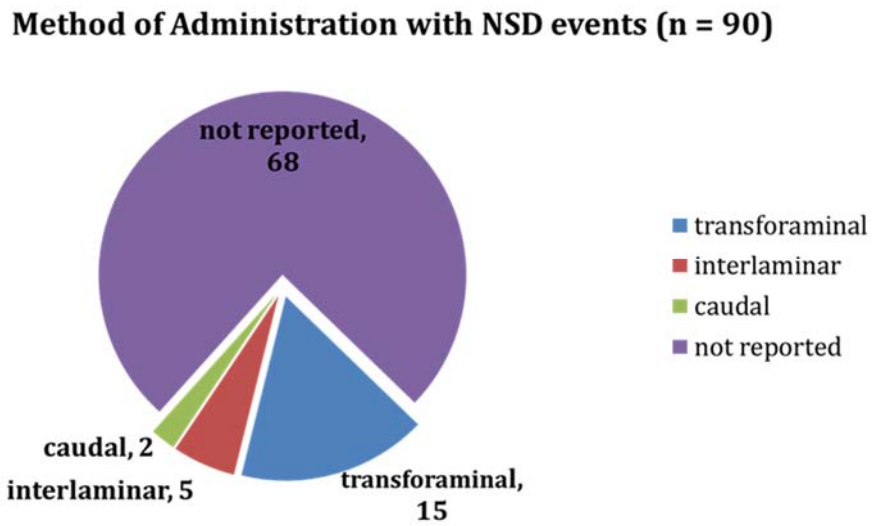


Reporting of Neurological FAERS Cases May be Overrepresented with the Transforaminal Route

Frequency of Transforaminal ESI, 2013

- Commercially insured (<65 yrs): 50% transforaminal
- Medicare (≥ 65 yrs): 48% transforaminal

Method of administration for Nervous System Disorder Adverse Events, when known



FDA has Specific Processes for Determining That a Product is Efficacious and Safe for its Intended Use

- In order to seek approval for an application for the epidural route of administration, a sponsor would need to submit an application with adequate data to demonstrate efficacy and safety in pain management
- FDA has a specific process for determining a drug's efficacy for a specific use
  - Generally, at least two adequate and well-controlled trials, each convincing on its own, are needed to establish efficacy.
  - The adequate and well-controlled trials are designed with a pre-specified primary efficacy endpoint and powered to show some clinically meaningful effect.
- FDA has a specific process for determining a drug's safety for a specific use
  - The International Conference on Harmonization established minimum numbers of patients to be exposed to a drug for the purposes of safety monitoring during a drug development program
  - Safety assessments rely on multiple streams of data including, but not limited to, adverse event collection, laboratory testing, and vital sign monitoring in clinical trials

Distinction Between FDA Regulatory Action and FDA Safe Use Initiative Activities

- Some of the criticism that FDA received posed the question as to why FDA did not wait to take a regulatory action (i.e., add the class Warning statement) until the Safe Use Initiative-facilitated expert work group completed their work
- FDA's regulatory mandate requires that we make prescribers and patients aware of serious or clinically significant adverse reactions that have occurred with a drug
  - When we issued the Drug Safety Communication and required the Warning statement, FDA had reached a point based on internal evaluation of the data that we needed to add a Warning
- The expert work group convened by the Safe Use Initiative is not a regulatory body, and had its own internal timeline for completing its work
- Furthermore, the expert panel's clinical considerations, intended to maximize the safe use of ESI, are meant to provide guidance for the medical community, and are not binding on FDA

Acknowledging the Input We've Gotten from Patients and the Medical Community on ESI Safety

- FDA appreciates the diverse input we have received through submissions to the advisory committee meeting docket and from speakers at the Open Public Hearing
  - Patients who have shared their stories of difficulties experienced following an ESI, including arachnoiditis or fungal meningitis and its complications
  - Patients who have benefited from treatment with ESI
  - Professional societies that have provided rationales for the place ESI holds in medical care
  - Individual members of the medical community who support the continued use of ESI as part of the treatment of spinal pain

Is a Better Evidence Base for ESI Safety in Development?

- In written submissions to the FDA docket for this meeting, some abstracts from a recent scientific meeting were cited
- The abstracts reported low incidences of adverse events from large cohorts (1000s of patients)
- The abstracts are extremely limited regarding information to assess how the adverse event monitoring was conducted
- The pain management community recognizes the need for better data, and hopefully full manuscripts will follow with the detail needed to assess the validity of the findings

April 23, 2014

FDA Drug Safety Communication: FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain

"…As part of FDA's ongoing effort to investigate this issue, we plan to convene an Advisory Committee meeting of external experts in late 2014 to discuss the benefits and risks of epidural corticosteroid injections and to determine if further FDA actions are needed."

What are the Options for Next Steps from a Regulatory Perspective?

- Revise the Prescribing Information of injectable corticosteroids
  - Possibilities include
    - Addition of a Contraindication
    - Addition of a Boxed Warning
    - Modification of the Warning statement
- Maintain the Prescribing Information as it currently reads

Prescribing Information

Prescribing information is written for healthcare providers and must:

- Contain a summary of essential scientific information needed for safe and effective use of drug
- Be informative and accurate and neither promotional in tone nor false or misleading in any particular
- Be updated when new information becomes available that causes labeling to become inaccurate, false, or misleading

See 21 CFR 201.56(a)

Contraindication

- Describes a situation in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit.
- These situations include the use of the drug in a subpopulation of patients that have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed.

Contraindications May Be Based On:

- Observed adverse reactions
  - The risk of the adverse reaction in the clinical situation to which the contraindication applies, based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to any patient

    AND
  - The causal relationship between exposure to the drug and the adverse reaction is well established.
- Anticipated adverse reactions supported by data (e.g., pharmacology, chemistry, or drug class data; or animal data) and the likelihood and severity of the adverse reaction

See *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf*

Boxed Warning

- Must:
  - Contain "contraindications or serious warnings, particularly those that may lead to death or serious injury"
  - Be first section in Full Prescribing Information
  - Be surrounded by a "box" (i.e., single black line)

See 21 CFR 201.57(c)(1)

Boxed Warning

- Ordinarily used in the following situations:
  - Adverse reactions that are so serious in proportion to potential benefit that it is essential it be considered in assessing risks and benefits of using a drug,

    OR
  - There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of drug,

    OR
  - Drug approved with restrictions to assure safe use because drug can be safely used only if distribution or use is restricted
- Can also be used in other situations:
  - To highlight a warning that is especially important to prescriber
  - For a drug that poses risk-benefit considerations that are unique among drugs in a drug class

See *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf*

Warnings and Precautions Section

- Should describe serious or clinically significant adverse reactions that occurred with the drug or risks that are expected to occur
- Each Warnings and Precautions section should include a succinct description of a topic and should include (if known):
  - Known risk factors for adverse reaction
  - Outcome
  - Numerical estimate of risk or adverse reaction rate
  - Steps to take to prevent, monitor, or manage an adverse reaction

See 21 CFR 201.57(c)(6) and
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf

Questions for the Committee

Question 1

DISCUSSION: Discuss your understanding of the evidence regarding the benefits of epidural corticosteroid injection administered to reduce inflammation for pain management. Considerations in the discussion may include the following:

a. Medical condition being treated
b. Location of the injection
c. Injection method
d. Corticosteroid formulation

Question 2

DISCUSSION: Discuss your understanding of the evidence regarding the risks of epidural corticosteroid injection administered to reduce inflammation for pain management, particularly the potential neurological sequelae. Considerations in the discussion may include the four factors listed in question 1 above.

a. Medical condition being treated
b. Location of the injection
c. Injection method
d. Corticosteroid formulation

Question 3

VOTE: Based on your discussions of the evidence regarding the benefits and risks of epidural corticosteroid injection administered to reduce inflammation for pain management, do you recommend that FDA add a contraindication to the labeling of injectable corticosteroids for the use of these products in epidural administration?

As per 21 CFR 201.57c(5), a drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication.

Question 3a.

DISCUSSION: Please explain the basis for your recommendation and any additional recommendations for other labeling changes (e.g., addition of a boxed warning, modification of the current warning statement, etc.).

Question 4

DISCUSSION: Discuss any additional recommendations you have on this topic.

Backup Slides Shown

Nonclinical Studies in Literature

- Pig study
  - intra-arterial administration of methylprednisolone acetate (MPA) or dexamethasone sodium phosphate (DSP) or prednisolone sodium succinate (PSS)
    - pigs who received MPA had serious neurologic sequelae
    - pigs who received DSP or PSS had no noticeable deficits
  - strong relationship with particulate steroids and observed CNS findings
  - limitations: small study (2-4 animals per group) and lack of vehicle control groups

Okubadejo GO et al. *J Bone Joint Surg Am*. 2008; 90:1932-8

Nonclinical Studies in Literature

- Rat study
  - Prospective in vivo study of intra-vascular injection
  - neurologic deficits and brain lesions observed with both particulates and non-particulates

	Depo-Medrol N=11	Depo-Medrol Carrier N=6	Solu-Medrol N=8	Decadron N=5	Normal Saline N=6
Neurologic Deficit	4	0	1	0	0
Brain Lesions	8	3	8	0	0
Evans Blue Leakage	+		+		0

Dawley JD et al. Spine. 2009; 34:1638-1643.